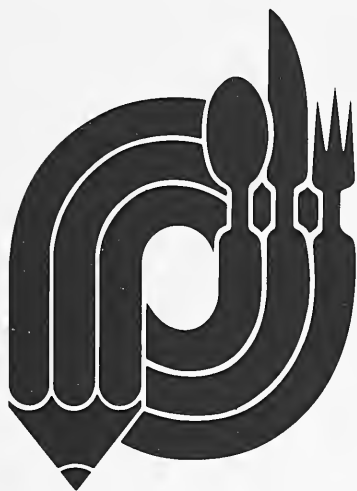


**Annual Report of the
National Institutes of Health**

**PROGRAM IN BIOMEDICAL
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RESEARCH AND TRAINING
FISCAL YEAR 1982**

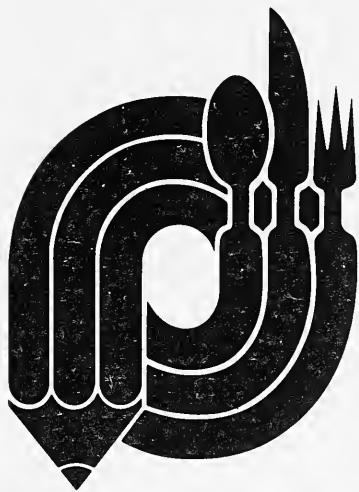


**NIH Nutrition
Coordinating Committee**

**U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health**

Annual Report of the
National Institutes of Health (U.S.)

**PROGRAM IN BIOMEDICAL
AND BEHAVIORAL NUTRITION
RESEARCH AND TRAINING
FISCAL YEAR 1982**



Prepared by
NIH Nutrition
Coordinating Committee

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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CONTENTS

	Page
THE MEMBERSHIP OF THE NUTRITION COORDINATING COMMITTEE	vii
THE MEMBERSHIP OF THE NCC SUBCOMMITTEE ON NUTRITION EDUCATION	ix
ACKNOWLEDGEMENTS	xi
PREFACE	xiii
L THE FY1982 PROGRAM IN BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING	1
DEFINITION OF NUTRITION RESEARCH AT THE NIH	3
FY 1982 OBLIGATIONS FOR NUTRITION RESEARCH AND TRAINING	3
Overview of the Nutrition Program	3
Comparison of Nutrition Program with Overall NIH Program	9
THE CLINICAL NUTRITION RESEARCH UNITS	10
THE EXTRAMURAL RESEARCH PROGRAM	12
The Research Program	12
Manpower Development	21
Program Development	25
Nutrition Conferences Sponsored by the NIH	32
THE INTRAMURAL RESEARCH PROGRAM	34
NUTRITION RESEARCH TRAINING	41
Extramural Training	43
Intramural Training	46
HIGHLIGHTS OF SPECIAL INTEREST AREAS IN NUTRITION	48
Nutrition and Prevention of Disease	50
Research on Vitamins	60
Behavioral Studies in Nutrition	66
Child and Infant Nutrition	75

	Page
Nutrition and Genetics	80
Epidemiological Research in Nutrition	85
Nutritional Status	89
Nutrition and Obesity	94
Nutrition Education Research	101
Total Parenteral and Enteral Nutrition	104
Maternal Nutrition	107
Nutrition Education for the Public	110
Nutrition and Aging	112
Nutrition Education for Professionals	114
International Research in Nutrition	116
II NUTRITION COORDINATING COMMITTEE	121
COMMITTEE STRUCTURE	123
COMMITTEE ACTIVITIES AND ACCOMPLISHMENTS	123
Scientific Seminars	123
The Videotape Series, "EAT WELL, BE WELL II"	134
Conferences Sponsored by the NCC	137
SUBCOMMITTEE ON NUTRITION EDUCATION ACTIVITIES AND ACCOMPLISHMENTS .	137
National Nutrition Month at the NIH, March 1982	138
NIH-NCC Nutrition Research Exhibit	139
III NUTRITION COORDINATING COMMITTEE OFFICE	141
ACTIVITIES OF THE NCC OFFICE	143
Congressional Hearings on Nutrition	143
Official Reports and Special Presentations on Nutrition . . .	144
The NCC Office-Clinical Center Study on the Long-Term Effect on Infants of Hypochloremic Metabolic Alkalosis Resulting from Infant Formulas Deficient in Chloride	145

	Page
DHHS Nutrition Research Initiative	146
The Joint Subcommittee on Human Nutrition Research of the Federal Coordinating Council for Science, Engineering and Technology, Office of Science and Technology Policy, Executive Office of the President	150
IV. APPENDICES	155
A. MANDATE OF THE NIH NUTRITION COORDINATING COMMITTEE	157
B. NUTRITION POLICY OF THE NIH	159
C. FY 1982 NUTRITION EXPENDITURES BY INSTITUTE AND DIVISION	161
D. LEGISLATIVE AUTHORITY OF NIH FOR HUMAN NUTRITION RESEARCH	173

LIST OF TABLES

	Page
I. NIH Biomedical and Behavioral Nutrition Research and Training, FY 1982, by Category of Support	4
II. Support Mechanisms for Clinical Trials, FY 1982	6
III. Interagency Reimbursement Agreements with Nutrition Research Components Funded by the NIH in FY 1982	8
IV. Comparison of Total NIH and Nutrition Obligations in the Three Major Components of Extramural Research, FY 1982	10
V. PA's, RFA's, and RFP's in Nutrition Research and Training Published in <u>The NIH Guide for Grants and Contracts</u> , FY 1982	26
VI. NIH Sponsored Nutrition Conferences, FY 1982	33
VII. NIH Training in Nutrition, FY 1982	42
VIII. Comparison of Total NIH and Nutrition Program Support of Extramural Research Training and Fellowships, FY 1978 - FY 1982	43
IX. Special Interest Areas in Nutrition--Summary Table	49

LIST OF FIGURES

1. FY 1982 Expenditures of NIH Program in Biomedical and Behavioral Nutrition Research and Training, by B/I/D	9
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Zekin Shakhashiri, M.D.

Consultant

Van Hubbard, M.D., Ph.D.
(Intramural NIADDK)

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As of September 30, 1982

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Division of Research Grants	John Schubert, Ph.D. (Julius A. Currie, Ph.D.)
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Food and Drug Administration	Allan Forbes, M.D. (John Vanderveen, Ph.D.)
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Dr. Henry Fukui

National Heart, Lung, and Blood
Institute

Ms. Marilyn Farrand

Office of Communication

Mr. Don Ralbovsky

ACKNOWLEDGEMENTS

On behalf of the Nutrition Coordinating Committee I wish to thank two members of the NCC Office staff: Ms. Karen Donato for her excellent work in updating the annual report, and Dr. Thomas Vogl for the extensive analysis of the program based on the computerized data retrieval system. Mrs. Sherri Wisner is especially thanked for her editorial and technical assistance in the final preparation of the report.

Artemis P. Simopoulos, M.D.
Chairman, Nutrition Coordinating Committee
Office of the Director
National Institutes of Health

PREFACE

The National Institutes of Health is the major agency in the Federal Government that supports research and training in nutrition as it relates to health maintenance, human development throughout the life cycle, disease prevention, and disease treatment. The NIH Program in Biomedical and Behavioral Nutrition Research and Training is supported by all 11 Institutes and one Division, namely:

- NCI - National Cancer Institute
- NHLBI - National Heart, Lung, and Blood Institute
- NIDR - National Institute of Dental Research
- NIADDK - National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
- NINCDS - National Institute of Neurological and Communicative Disorders and Stroke
- NIAID - National Institute of Allergy and Infectious Diseases
- NIGMS - National Institute of General Medical Sciences
- NICHD - National Institute of Child Health and Human Development
- NEI - National Eye Institute
- NIEHS - National Institute of Environmental Health Sciences
- NIA - National Institute on Aging
- DRR - Division of Research Resources

The membership of the NCC consists of representatives from the 11 Institutes and the Division that support nutrition research. Additional NIH offices, other agencies of the Public Health Service and the Department of Health and Human Services, and the Office of Science and Technology Policy in the Executive Office of the President have liaison representatives to the committee. The Nutrition Coordinating Committee (NCC) operates out of the Office of the Director, NIH.

The NIH nutrition program includes extramural and intramural research and research training, and research manpower development. The major component of the NIH nutrition program is the extramural research program carried out at various universities; in graduate science departments, principally departments of nutrition; and in medical, dental, and other health professional schools, especially schools of public health. The

NIH intramural program in nutrition research is carried out on the NIH campus in Bethesda, Maryland, primarily at the Clinical Center, with the exception of the programs of two Institutes: The intramural program of the National Institute on Aging is carried out at the Gerontology Research Center in Baltimore, Maryland, while that of the National Institute of Environmental Health Sciences is located in Research Triangle Park, North Carolina.

Nutrition is an important, crosscutting program area within the NIH. For this reason, the nutrition program is coordinated through the NIH Nutrition Coordinating Committee that operates out of the Office of the Director and is advisory to the Director. The mandate of the Nutrition Coordinating Committee is to review, stimulate, and encourage the necessary support of nutrition research and training in order to better define the role of nutrition in the promotion of health, and the prevention and treatment of disease. As one of the committees that oversees selected "trans-NIH health problems," the Nutrition Coordinating Committee meets annually (or as required) with the Director, NIH, to review progress and plans in nutrition research.

The committee is the focus for the review of nutrition research and training priorities, their coordination, and for the development of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. This focus minimizes duplication of effort among the Institutes and identifies areas where research, research training, and research manpower development in nutrition need to be advanced. This is accomplished through joint program announcements (PA's) and requests for applications (RFA's) developed by the committee and sponsored by more than one Institute. Committee representatives are also encouraged to have their individual Institutes develop program announcements, requests for applications, and requests for proposals (RFP's). In FY 1982, the Institutes continued to emphasize the nutrition research program through the publication in the NIH Guide for Grants and Contracts of seven program announcements, seven requests for applications, and one request for proposals.

The committee plays a key role in the development of nutrition policy at the NIH. Currently, nutrition policy at the NIH emphasizes eight critical areas. Research is emphasized in four of these critical areas: clinical nutrition throughout the life cycle; the role of nutrition in disease development; prevention of disease; and treatment of disease. The other four critical areas are the transfer of modern nutrition technology, nutrition education for professionals and the public, nutrition research training and research manpower development in nutrition, and the coordination of all these activities. Each year, the NCC prepares the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training for the preceding fiscal year and sponsors a major conference or workshop in nutrition that includes the interests of many Institutes. The proceedings of this conference are published. In addition to coordinating the NIH nutrition program, the NCC office staff is also assigned additional responsibilities that include responding to requests for information on nutrition from Congress and from other Federal agencies.

During FY 1982, the NCC office continued to serve as the executive secretariat for the Joint Subcommittee on Human Nutrition Research (JSHNR) that is cochaired by a representative of USDA, and by the NCC Chairman representing DHHS. The NCC Chairman also has been designated by the Secretary, Health and Human Services (DHHS), as the "initiative coordinator for the Health Research Initiative on Nutrition Research. The purpose of the Nutrition Research Initiative is to develop a cohesive program for DHHS in nutrition research and training so that the precise role of nutrition in health and disease can be defined and that appropriate mechanisms emerge for the prevention and proper management of disease. The health research initiatives are experiments in cooperative research, planning, and implementation by DHHS agencies and represent efforts to strengthen research through cooperative planning and information exchange on a continuing basis.

Part I of the report presents the FY 1982 Program in Biomedical and Behavioral Nutrition Research and Training in two sections. The first section begins with the definition of nutrition research at the NIH, and then focuses on the FY 1982 obligations for nutrition research and training. The analysis of the fiscal aspects of the program include an overview of the nutrition program and a comparison of actual obligations for nutrition with NIH obligations as a whole.

The second section consists of narrative descriptions beginning with a brief description of the Clinical Nutrition Research Units and a summary of their second annual meeting, which was held in FY 1982. Descriptions of the extramural and intramural research programs, and the nutrition research training program follow. Expanded descriptions of "Highlights of the Special Interest Areas in Nutrition" emphasize research of particular scientific interest. The 15 special interest areas, in decreasing order of expenditure, are: Nutrition and Prevention of Disease, Research on Vitamins, Behavioral Studies in Nutrition, Child and Infant Nutrition, Nutrition and Genetics, Epidemiological Research in Nutrition, Nutritional Status, Nutrition and Obesity, Nutrition Education Research, Total Parenteral and Enteral Nutrition, Maternal Nutrition, Nutrition Education for the Public, Nutrition and Aging, Nutrition Education for Professionals, and International Research in Nutrition.

Part II of the report describes the structure of the NIH Nutrition Coordinating Committee, the charge of the Subcommittee on Nutrition Education, and highlights of the committee's and subcommittee's activities and accomplishments in FY 1982.

Part III describes the major responsibilities and activities of the NCC office. These activities encompass: responding to information requests about nutrition in general and about the NIH nutrition program in particular from the Congress, other Federal agencies, the scientific community and the public; collaborating in the Clinical Center Intramural Research Study on the Long-Term Effect on Infants of Hypochloremic Metabolic Alkalosis Resulting from Infant Formulas Deficient in Chloride; coordinating the Departmental Research Initiative in Nutrition; representing NIH in various nutrition activities under way at the Office of the Assistant Secretary for Health; and serving as the Executive Secretariat of the

Joint Subcommittee on Human Nutrition Research of the Committee on Health and Medicine and the Committee on Agriculture, Food, and Forestry Research of the Federal Coordinating Council for Science, Engineering and Technology, Office of Science and Technology Policy in the Executive Office of the President.

Part IV consists of four appendices: appendix A includes the mandate of of Nutrition Coordinating Committee; appendix B presents the nutrition policy of the NIH; appendix C presents the FY 1982 nutrition expenditures of the Institutes and DRR by support mechanism; and appendix D includes the legislative authority of NIH for human nutrition research.

FY 1982 was indeed a time of major accomplishments for the Nutrition Coordinating Committee and the office. The cooperative and collaborative spirit that the NCC fosters was dramatically illustrated by a number of events that involved not only the NIH Institutes and Divisions but also other Public Health Service (PHS) agencies and Federal agencies outside of DHHS.

During this period, the DHHS Nutrition Research Initiative (NRI) was firmly established. The NRI was inaugurated by Secretary Sceweiker at the Conference on the Assessment of Nutritional Status. In his conference address, Secretary Schweiker said: "Your being here today to launch a special Research Initiative on Nutrition shows we can break new ground, and build on our progress thus far. For the first time we are pulling together on a formal basis to bolster our research efforts. In addition to the National Institutes of Health, we will draw on studies done by the Food and Drug Administration; the Alcohol, Drug Abuse and Mental Health Administration; the Centers for Disease Control; and the National Center for Health Statistics." Other Federal agencies, including the United States Department of Agriculture, the Veterans Administration, and the Department of Defense, the scientific community, and industry actively participated in all phases of the conference. The proceedings of the conference were published as a supplement to the Am. J. Clin. Nutr. (35:1089-1325, May 1982).

The workshop on Body Weight, Health, and Longevity, also held under the auspices of the DHHS Nutrition Research Initiative on January 25-26, 1982, was cosponsored by NIH and the Centers for Disease Control (CDC) with the participation of other Government agencies, the scientific community, and industry. The workshop was motivated by the growing public health concern regarding the prevalence of obesity in the United States, the availability of new data from the Framingham Heart Study, and the fact that the terminology of body weight standards requires clarification. The workshop concluded that the interpretation of studies on body weight, morbidity, and mortality must be undertaken with careful attention to (1) the methods used to define overweight or relative weight, (2) exclusions for pre-existing morbid conditions, (3) the length of observations of subjects, and (4) confounders in the analysis.

The joint program announcement "NIH New Investigator Research Award (NIRA) in Nutrition: ADAMHA Special Notification for Research on Nutrition and Behavior," published in FY 1981, marked the first time that a

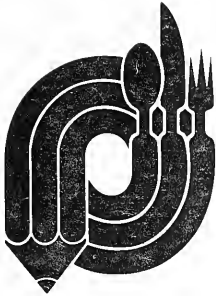
joint PA in nutrition had the support of NIH (NCI, NIADDK, NICHD, and NIDR) and another agency of the PHS, ADAMHA.

These activities reinforced the great spirit of cooperation that has been developed among the PHS agencies and the NIH Institutes. It is important to note that it would not have been possible to prepare this report without the interest and support of the NCC members, who provided descriptions of nutrition research highlights and accomplishments along with the fiscal information for their respective nutrition programs.

Plans are already in place for more program announcements and conferences to be sponsored by the Institutes and the NCC office. We look forward to the next year with the anticipation of continued effective collaboration.

A handwritten signature in cursive script, reading "Artemis P. Simopoulos M.D.", written in dark ink.

Artemis P. Simopoulos, M.D.
Chairman,
Nutrition Coordinating Committee
Office of the Director, NIH



I.

THE FY 1982 PROGRAM IN BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING

The Program in Biomedical and Behavioral Nutrition Research and Training is based on a common definition of nutrition research and a computerized data retrieval system developed by the Nutrition Coordinating Committee. The expansion of the program is the result of a number of requests for applications, requests for proposals and various program announcements developed by the Institutes themselves or jointly with the Nutrition Coordinating Committee. The program is presented in terms of the financial obligations in nutrition by category of support. The description of the program includes 15 special interest areas that were selected on the basis of scientific progress and political interest.

The NIH nutrition program is supported by the 11 Institutes and the Division of Research Resources (DRR) and is coordinated through the Nutrition Coordinating Committee. The program supports research and research training in nutrition as it relates to health maintenance, human development throughout the life cycle, disease prevention, and disease treatment.

DEFINITION OF NUTRITION RESEARCH AT THE NIH

Included in the first Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, FY 1977 issued by the NCC was the definition of biomedical and behavioral nutrition research that the NCC developed. That definition, which continues to serve as a basis for data retrieval and for the assessment of information about the nutrition research and training activities of the NIH, is as follows:

"The term nutrition research includes studies designed to assess the consequences of food or nutrient intake and utilization in the intact organism, including man, and the metabolic and behavioral mechanisms involved. These studies encompass investigation of nutrient variables at the cellular or subcellular level. This definition also includes:

- ° Research designed to elucidate the metabolic role or function of nutrients in both animal models and man.
- ° All studies concerned with genetic-nutrient-environmental interactions where a nutrient is a variable.
- ° Dietary studies expected to produce significant changes in health status, including the maintenance of health and the treatment of disease in man. Such studies might include clinical trials, epidemiological studies, metabolic studies, surveillance, and nutritional status monitoring studies."

FY 1982 OBLIGATIONS FOR NUTRITION RESEARCH AND TRAINING

Overview of the Nutrition Program

For FY 1982, the total NIH actual obligation in biomedical and behavioral nutrition research and training was \$144,323,000. Actual obligations in nutrition by each Institute and applicable Division are as follows:

NCI	\$30,553,000	NIHMS	\$ 1,841,000
NHLBI	35,449,000	NICHD	18,356,000
NIDR	1,529,000	NEI	5,256,000
NIADDK	26,981,000	NIHES	1,582,000
NINCDS	2,839,000	NIA	3,261,000
NIAID	1,853,000	DRR	14,823,000

TABLE I

National Institutes of Health
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982,
BY CATEGORY OF SUPPORT
(Actual Obligations, in thousands of dollars)

Extramural	Item	Breakdown		Total	
		Number	Cost	Number	Cost
Research grants:	Regular	1,199	71,138		
	Clinical trials	119	6,240		
	Total			1,318	77,378
Program projects:	Regular	77	14,821		
	Clinical trials	6	1,678		
	Total			83	16,499
Contracts:	Regular	120	5,771		
	Clinical trials	28	2,417		
	Total			148	8,188
Centers:	Regular	66	12,244		
	Clinical trials	0	0		
	Total			66	12,244
Research Resources Support				262	14,864
Reimbursement agreements				15	1,243
Research Career Development Awards				58 *	1,361
New Investigator Research Awards				60 *	1,900
Training:	Training grants	307 *	2,419		
	Fellowships	38 *	415		
	Total			345 *	2,834
Subtotal - Extramural					\$ 136,511
<u>Intramural</u>					
Projects				85	7,364
Training				24 *	448
Subtotal - Intramural					\$ 7,812
TOTAL NUTRITION RESEARCH AND TRAINING - NIH					\$ 144,323

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table I presents the FY 1982 nutrition obligations by category of support for the NIH as a whole, and appendix C contains the obligations for each Institute and DRR (Tables C-1 through C-12).

To determine obligations for nutrition research and training, the Institutes' program staff reviews all research grants and contracts in order to identify the portion of the project with a nutrition component, in accordance with the definition of nutrition research, and then determines the percentage applicable to nutrition. The NIH has thus been able to eliminate such confusing and easily misunderstood terms as "primary/secondary," "major/minor," "nutrition related," and "direct/indirect" in referring to its nutrition program. The NCC office has developed a computerized data retrieval system for the storage and analyses of data on nutrition research and training activities of the NIH. The data base is updated periodically and cross-checked against the NIH grant information and accounting system, IMPAC (Information for Management Planning, Analyses, and Coordination). This computer system has enabled the NCC office to carry out detailed analyses in terms of percentage of the nutrition component, support mechanism (contract, type of grant, etc.), and special interest area. Other analyses are performed on an ad hoc basis. The actual obligations for extramural research, training, and manpower development account for \$136,511,000 while intramural research and training account for \$7,812,000.

The extramural program is classified by mechanism of support into regular research grants, program projects, contracts, and centers. Clinical trials are funded by all four of these mechanisms. Research resources support, reimbursement agreements, research career development awards, new, academic and teacher investigator awards, and training (training grants and fellowships) are also included in the extramural program. The intramural program consists of research projects and training (fellowships).

Research grants support a discrete, specified, circumscribed project to be performed by investigator(s) in areas representing specific interests and competencies. Such research is initiated entirely by investigators outside the NIH. In FY 1982, the NIH supported 1,318 research grants with nutrition components for a total obligation of \$77,378,000. This category constitutes the largest single area of support in nutrition.

Program projects are also investigator initiated research, but differ from research grants in that they are awarded for the support of a broadly based, multidisciplinary, often long-term research program that has a specific major objective or a basic theme. A program project generally involves the organized efforts of relatively large groups, members of which are conducting research projects designed to elucidate various aspects or components of the major objective. In FY 1982, 83 program projects were funded for \$16,499,000.

Contracts are initiated by the agency to develop or apply new knowledge or to test, screen, or evaluate a product, material, device, or component for use by the scientific community. In FY 1982, NIH funded 148 contracts with nutrition research components for \$8,188,000.

Centers are an additional component of agency initiated research, and they support any part of a full range of research and development from very basic to clinical. Centers may involve ancillary supportive activities, such as protracted patient care, necessary to the primary research effort. The spectrum of activities comprises a multidisciplinary approach to a specific disease entity or biomedical problem area. In FY 1982, NIH obligations for the 66 centers with a nutrition research component were \$12,244,000.

Investigator initiated research (research grants and program projects) in FY 1982 amounted to \$93,877,000, whereas agency initiated research support in nutrition (contracts and centers) was \$20,432,000. Thus direct support for nutrition research was predominantly investigator initiated. The \$93.9 million obligated for investigator initiated nutrition research in FY 1982 was 65 percent of all nutrition research and training obligations in that fiscal year. Obligations for agency initiated research (contracts and centers combined) were \$20.4 million or 14 percent of total FY 1982 obligations for nutrition research and training.

Clinical trials in nutrition are supported by each of the four major mechanisms discussed above--research grants, program projects, contracts, and centers. A clinical trial is defined as a scientific research activity undertaken to define, prospectively, the effect and value of prophylactic/diagnostic/therapeutic agents, devices, regimens, procedures, etc., applied to human subjects. The study must be prospective, and intervention of some sort must occur. The number of cases or patients depends on the hypothesis being tested, but must be sufficient to permit anticipation of a definite, statistically significant, result. Phase I, feasibility, or pilot studies are excluded by definition.

FY 1982 obligations in support of 153 clinical trials with nutrition components totaled \$10,335,000. These obligations constitute 7.2 percent of total nutrition obligations for FY 1982. The distribution of clinical trials among the four support mechanisms is displayed in table II.

TABLE II
SUPPORT MECHANISMS FOR CLINICAL TRIALS, FY 1982
(dollars in thousands)

<u>Funding Mechanism</u>	<u>Number of Clinical Trials</u>	<u>FY 1982 Expenditures</u>
Research Grants	119	6,240
Program Projects	6	1,678
Contracts	28	2,417
Centers	<u>0</u>	<u>0</u>
TOTAL	153	10,335

Research resources support is provided by the Division of Research Resources and NICHD. For FY 1982, a total of \$14,864,000 was devoted to this category of the NIH nutrition program. The DRR research resources support of \$14,823,000 is provided through five mechanisms:

1. The General Clinical Research Centers Program, with nutrition obligations of \$11,533,000 in FY 1982, constitutes the bulk of DRR general research support. These centers foster the development of technological and therapeutic advances to expedite the application of basic biological knowledge into effective patient care.

The balance of \$3,290,000 is provided through the following four mechanisms:

2. The Animal Resources Program provides a unique institutional research environment for the use of nonhuman primates or other animals in multicategorical research.
3. The Biomedical Research Support Program responds to emerging research opportunities and allows the supported institution self-determination in the development and conduct of pilot and other small projects.
4. The Biotechnology Resources Program attempts to interface the knowledge of the physical sciences, mathematics, and engineering with biology and medicine.
5. The Minority Biomedical Support Program provides funds to ethnic minority institutions to conduct research.

Reimbursement agreements are entered into between the NIH and other Federal agencies. In FY 1982, 15 such agreements were made in the area of nutrition by three Institutes, with total obligations of \$1,243,000. The 15 reimbursement agreements are listed in table III.

Manpower development in nutrition research is furthered through research career development awards and through new investigator research awards. In FY 1982, 10 Institutes supported 118 individuals at a total cost of \$3,261,000 by these mechanisms.

Training in biomedical and behavioral research is supported by NIH through national research service awards. Training grants are awarded to institutions; fellowships are awarded to individuals. Eight Institutes support extramural training grants in nutrition research awarded to institutions for the support of training of individuals selected by the institutions, while six Institutes awarded fellowships in nutrition research to individual applicants. A total of 345 extramural trainees and fellows were supported for a total of \$2,834,000. (See also table VII.)

Intramural research and training was carried out by nine Institutes with a total obligation of \$7,812,000, of which \$448,000 was devoted to training (fellowships) by four Institutes.

TABLE III

INTERAGENCY REIMBURSEMENT AGREEMENTS WITH NUTRITION RESEARCH
COMPONENTS FUNDED BY NIH IN FY 1982

NCI	<ul style="list-style-type: none"> - Followup of the National Health and Nutrition Examination Survey (with National Center for Health Statistics) - In Vitro Transformation of Epidermal Cells (with Department of Energy at Oak Ridge National Laboratory) - In Vitro Quantification of Nitrogen by Whole Body Neutron Action (with Department of Energy at Brookhaven National Laboratory) - Chemoprevention of Epithelial Cancer by Retinoids (with Department of Energy at Brookhaven National Laboratory) - NHANES I Epidemiologic Followup Survey (with National Center for Health Statistics.) - Research on Occupational Carcinogenesis (with National Institute of Occupational Safety and Health) - Epidemiological Studies of Cancer in Alaskan Natives (with CDC)
NHLBI	<ul style="list-style-type: none"> - Analyze Human Serum Samples on Diet Study & Metabolism (with Department of Energy, Germantown) - CDC-NHLBI HDLC Standardization Program (with CDC) - Technical Resources for Basic Analytical Techniques (with CDC) - Food Fatty Acid Analysis and Evaluation (with U.S. Department of Agriculture) - Services and Resources Provided by CDC for NHLBI (with CDC) - Lipid Research Clinics Program (with CDC) - Data on Nutrient Content of Foods in American Diet (with U.S. Department of Agriculture)
NIA	<ul style="list-style-type: none"> - Followup Study of U.S. Health and Nutrition Examination Survey (HANES) Respondents (with NCHS)

Figure 1 presents an overview of these data, displaying each Institute's and DRR's obligations in nutrition research and training. In this figure, the total obligation of each Institute is divided into five components. The three lowermost components of each bar, taken together, represent each Institute's total obligation for extramural nutrition research. These three components represent: those grants and contracts with a nutrition component less than 50 percent of the entire grant or contract; those with a nutrition component of 50 to 99 percent; and those that are entirely (100 percent) nutrition research. The other two components depicted in each bar represent: 1) training grants and fellowships and 2) intramural research (the top component of each bar).

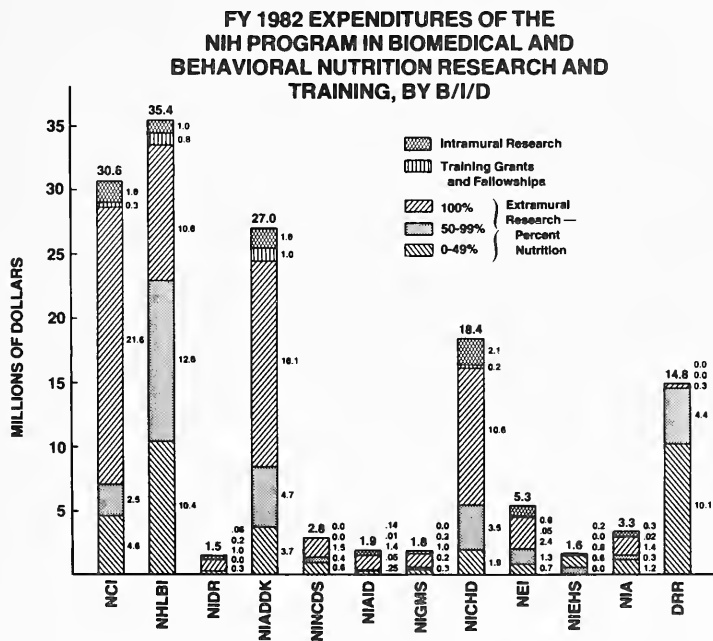


Figure 1

Comparison of Nutrition Program With Overall NIH Program

The entire NIH appropriation for FY 1982, i.e., continuing resolution, was \$3,641,875,000; in comparison, the nutrition obligation of \$144,323,000 is 4.0 percent of the total NIH budget. The nutrition component of NIH research grants and program projects was 5 percent, of contracts 2.5 percent, and of centers 3.5 percent. As can be seen from table IV, research grants and program projects (investigator initiated research) account for 73 percent of the NIH extramural research component and 82

percent of the nutrition budget. This indicates that investigator initiated research is the predominant component of the research of both the agency and the nutrition program. Contracts represent 13 percent for NIH and 7 percent of the nutrition program, while centers represent 14 percent for NIH as a whole and 11 percent for the nutrition program. This suggests that with respect to contracts and centers, the nutrition program lags behind NIH programs as a whole.

TABLE IV
COMPARISON OF TOTAL NIH AND NUTRITION OBLIGATIONS IN THE THREE
MAJOR COMPONENTS OF EXTRAMURAL RESEARCH, FY 1982
(in thousands of dollars)

	NIH Total	Nutrition Program
Research grants and program projects	1,832,867 (73%)	93,877 (82%)
Contracts	320,537 (13%)	8,188 (7%)
Centers	<u>349,091</u> (14%)	<u>12,244</u> (11%)
TOTAL (of the three components)	2,502,495 (100%)	114,309 (100%)

THE CLINICAL NUTRITION RESEARCH UNITS

Since 1979, the NIH has supported a new National Program in Clinical Nutrition Research based on Clinical Nutrition Research Units (CNRU). A CNRU is an integrated array of research, educational, and service activities that is oriented toward human nutrition in health and disease. These units are funded jointly by NIADDK (five units) and NCI (two units).

The NIH has traditionally sponsored the component activities of CNRU's through a variety of award mechanisms, the principal ones having been research project grants and support for research training. The present initiative, core grants for shared facilities, has become an invaluable addition, especially in promoting multidisciplinary interactions. This approach also tends to ensure that a given CNRU has multiple sponsors, both Federal and non-Federal, thereby reducing the likelihood that it will become unduly dependent upon any one source for its continuing operation. Funding for educational programs and nutritional support services (patient care) are generally sought from sources other than NIH.

The specific objectives of the CNRU are:

1. To create or strengthen foci in biomedical research institutions for multidisciplinary research in clinical nutrition in order to

develop new knowledge about specific nutrients in health, human development, and the prevention and treatment of disease.

2. To strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and paramedical personnel in clinical nutrition.
3. To enhance patient care and promote good health by focusing attention towards clinical nutrition and generating nutritional information for the public.

A CNRU, at a minimum, must comprise the following seven components:

1. Research with human subjects and populations,
2. Laboratory investigations,
3. Research training,
4. Shared facilities and research services,
5. Education programs for medical students, house staff, practicing physicians, and paramedical personnel,
6. Nutritional support services, and
7. Public information activities.

The CNRU directors meet annually at the NIH with NIH staff. The purpose of the annual meeting is to facilitate communication, review research findings and problems, and discuss administrative concerns and constraints.

The first annual meeting of the CNRU directors was held December 3, 1980, at the NIH. The second annual meeting, held at the NIH on December 17, 1981, was considered a great success by the CNRU directors and NIH personnel in attendance. At this meeting, the importance of collaborative efforts in research methods and education activities that could be mutually reinforcing, acceptable, and useful to all seven CNRU's was emphasized. The following three areas of potential opportunity for institutional collaboration were discussed: clinical research, laboratory methods and services, and education and outreach activities. It was apparent that the CNRUs are effectively integrating nutrition components into many research projects, curriculum and patient care activities, as well as in the development of nutrition education materials for the public.

Highlights of the nutrition research programs of each of the seven CNRU's were presented at the first "Annual Conference of Human Nutrition Research Units--An Information Exchange Activity of the JSHNR," held on December 16-17, 1982 in Washington, D.C. The agenda planning meeting for this conference is described in detail on pages 153-4 of this report.

THE EXTRAMURAL PROGRAM

The major component of the NIH nutrition program is the extramural research program carried out at various universities; in graduate science departments, principally departments of nutrition; and in medical, dental, and other health professional schools, especially schools of public health.

The Research Program

Nutrition research supported by NIH includes the effects of nutrients on human growth and development, health maintenance and promotion, disease prevention, and disease treatment. The primary nutrition mission of NIH lies in biomedical and behavioral research and training; however, NIH also funds nutrition education for professionals and the public as an integral part of many research programs. NIH provides the public with nutrition pamphlets, public service announcements on radio and television, and materials for magazine articles. Nutrition education for professionals is provided through various scientific publications, conferences, and workshops. Appendix D describes the Institutes' legislative authorities for nutrition research.

NCI, NHLBI, NIDR, NIADDK, NINCDS, NIAID, NIGMS, NICHD, NEI, NIEHS, NIA, and DRR support research on requirements and basic metabolism of nutrients, the assessment of nutritional status of patients and populations, and the role of nutrition in health promotion and disease prevention. Following is a brief overview of the extramural activities of these Institutes.

The National Cancer Institute supports studies on the role of specific nutrients, both nutrient deficiencies and excesses, as well as overall nutritional status on the initiation and promotion of cancer in the hope of discovering clues to aid in the prevention, and treatment or regression of the disease. Projects in cancer etiology, biology, diagnosis, prevention and treatment are carried out in hospitals, research centers and universities within the United States and abroad.

Studies examine the relationship of various dietary components on the mechanisms of carcinogenesis, i.e., promotional phases of neoplastic cell evolution and growth, carcinogen sequestration in the gastrointestinal tract, and immunocompetence capacity as related to carcinogen exposure and subsequent neoplastic cell growth. The nutrients being studied for their anticarcinogenic properties include the vitamins A, E, K, C, and B₆, as well as zinc, selenium, and fiber. The relationship of fat intake, alcohol consumption, coffee, and specific food additives such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and saccharin to carcinogenesis is also being investigated.

Studies continue to explore the question of whether dietary components serve as risk factors apart from other environmental factors in the etiology of various site specific cancers. A number of epidemiological case control studies focus on the relationship of the various dietary components to cancer of the bladder, colon, lung, pancreas, stomach, breast, skin, esophagus, and oral cavity. Tumor registry data are also being used to address this possible relationship.

In a recent study of metastatic colorectal cancer patients, glucose tolerance was impaired and basal lactate production was increased. These changes were found to exist independently of each other. In response to hyperalimentation and total parenteral nutrition, lactate production increased in both cancer patients and controls, while oxygen production also increased significantly in the cancer patient. Indirect calorimetry measures have revealed elevated basal metabolic rates for lean body mass in cancer patients. Malnourished cancer patients appear to be deficient in anabolic hormones, have excessive amounts of anti-insulin hormones and inappropriately elevated triiodothyronine levels. In order to provide the proper nutritional support to the cancer patient, studies are under way on the abnormalities of glucose and lactate metabolism, the increased basal metabolic rates, and the overall nutritional status of the cancer patient.

The development of methods and tools for the nutritional assessment of cancer patients is important for understanding the effect of nutritional support on tumor response, tolerance to chemotherapy, performance status, and overall survival. Information on limb fat, muscle and bone volume now available from the computerized tomography (CT) scan is an important part of the evaluation and management of malignancy in various nutritional states. Evaluation of nutritional support procedures and related social and behavioral changes as they apply to the prevention and treatment of anorexia, malnutrition and cachexia in cancer patients is also under way.

Research in genetics supported by NCI involves in vivo and in vitro observations of aflatoxin metabolism, the manipulation of amino acids, and the development of methods to discriminate markers specific to the cancer-prone genotype. The use of human cells to test and predict cancer risks has important implications for the identification of high risk patients in the general asymptomatic populations.

The NCI also supports two Clinical Nutrition Research Units (CNRU), one at the University of Alabama in Birmingham and the other at the Memorial Sloan-Kettering Cancer Center. Basic nutrition research under way at these units includes studies on the effect of malnutrition on immune mechanisms, the relationships between zinc deficiency and immunological function, the requirements for folic acid coenzymes in purine biosynthesis, the use of oral and tube feedings to head and neck patients undergoing radiation therapy, and the selenium requirements for patients on parenteral nutrition.

The National Heart, Lung, and Blood Institute supports extramural nutrition research under the auspices of three divisions: the Division of Heart and Vascular Diseases, the Division of Blood Diseases and Resources, and the Division of Lung Diseases. A major portion of this research involves nutrition's role in hypertension, atherosclerosis and coronary heart disease, however, sickle cell disease, infantile respiratory distress syndrome and pulmonary function are also being investigated.

The Division of Heart and Vascular Diseases supports research on the role of diet in the epidemiology, etiology and prevention of cardiovascular disease. A number of epidemiology projects are studying the association

of diet to the coronary heart disease factors of serum cholesterol and blood pressure and in certain geographic areas in terms of cardiovascular disease morbidity, and mortality. Basic research studies consider the effect of diet and heredity on the structure and function of lipoproteins, on the metabolism of lipids and lipoproteins, and on the progression and regression of the atherosclerotic plaque process. Community health education demonstration and intervention projects apply much of the knowledge gained from the epidemiological and basic research studies, and examine the effect of nutrition education on changes in dietary habits and the subsequent prevention or modification of cardiovascular disease risks. For example, nutrition intervention studies under way in the workplace, in clinical practice, and in the school systems investigate the role of suggested dietary changes in lowering blood cholesterol, low density lipoproteins, triglycerides and blood pressure. These changes in risk factors are then considered in terms of the possible prevention and control of hyperlipidemia, atherosclerosis, and hypertension. Research continues on the development of appropriate nutrition education programs and adherence strategies that help to reduce the diet-related risk factors for hypertension, obesity, and cardiovascular disease.

Dietary intervention studies attempt to determine the success of controlling blood pressure by nonpharmacologic means; to assess changes in peripheral vascular resistance in response to dietary sodium; and to develop quantitative methods for estimating sodium intake by measuring the excretion of sodium.

Research on nutrition's role in sickle cell disease and in thrombosis receives support from the Division of Blood Diseases and Resources. Research on sickle cell disease aims to define the effect of various nutrients on red cell physiology, as well as the contributions of vitamin and mineral deficiencies to growth retardation and immunologic function in patients with the disease. Studies on thrombosis and hemostasis investigate the role of dietary lipids on platelet structure and function.

Infantile respiratory distress syndrome (RDS) is the single most frequent cause of death during the neonatal period. Research in this area, a priority of the Division of Lung Diseases, includes studies on maternal nutritional status as a means of reducing the risk of premature birth and subsequent risk of RDS. In addition, investigators are considering the influence of nutrition on lung defense functions such as the pulmonary alveolar macrophage and lung antioxidant enzymes. Since individuals with chronic obstructive lung disease are often malnourished, studies are under way to explain how malnutrition influences resistance to pulmonary infections, respiratory muscle fatigue, and lung surfactant function.

The National Institute of Dental Research supports research on the relationship between diet and nutrition, and the development and maintenance of both hard and soft tissues of the oral-facial complex. Special interests are in the problems of tooth and gingiva development and maintenance, periodontal diseases, and dental caries. The NIDR's National Caries Program focuses on the development of a measure of the cariogenicity of various foods, the relationship of human diet to caries development, the development of noncariogenic sweeteners, and the development of a

slow release oral fluoride device. The use of fluoride in preventing dental caries has been established and the NIDR continues to study the metabolic effects of various fluoride levels in humans as well as the mechanisms by which fluoride induces caries resistance.

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases supports basic and clinical nutrition research that focuses on the function and requirements of specific nutrients, and the relationship of these nutrients and overall diet to health promotion, disease prevention, and disease treatment. In general, basic research on the metabolism of nutrients and their interactions deals primarily with specific nutrients rather than a particular disease, organ, or stage of life cycle. Studies are under way on the metabolic role of specific dietary components, i.e., the essential amino acids and protein, carbohydrate, essential fatty acids and other lipids, vitamins, minerals, and dietary fiber. For example, tryptophan, tyrosine, and choline are being studied for their role in the formation of the neurotransmitters, serotonin, dopamine, and acetylcholine, respectively, as well as the subsequent effect on blood pressure, depression and tardive dyskinesia. Noninvasive stable isotopes are being used to study the effect of dietary protein and energy intake on whole body amino acid metabolism with particular emphasis on alanine, glycine and leucine. This research has opened up new approaches to estimating the amino acid requirements of healthy adults.

Studies on the trace minerals, i.e., iron, zinc, selenium, copper, silicon, chromium, tin, aluminum, molybdenum, magnesium, calcium and phosphorous, provide important data on their metabolism, interrelationships, and overall relationship to human health. Imbalances or inadequacies of certain trace minerals are likely to promote metabolic adaptations that lead to chronic disease. Research continues on iron deficiency, particularly in terms of work performance and exercise capacity, as well as changes in the red blood cells. Zinc status of certain segments of the population may reflect dietary inadequacies. Studies on dietary fiber examine its effect on stool transit time, digestion, rate of absorption, intestinal microflora, and interactions with nutrients, drugs, bile salts, and other substances.

Fundamental research on the mechanism of action of nutrients in absorption and metabolism, biological control of these processes, and the identification of other possible roles of nutrients and their metabolites provide important insight to the role of diet in the etiology of major diseases.

The clinical investigations supported by NIADDK relate to the assessment of nutritional status, the use of various nutritional support modalities, total parenteral nutrition, nutrient-drug interactions, and various diseases or conditions, such as obesity, diabetes, osteoporosis, anemia, atherosclerosis, end stage renal disease, and alcoholism.

A major research priority of NIADDK is the investigation of the underlying causes of obesity with particular emphasis on prevention and control. Studies investigate the regulation of fat cell size and fat metabolism; fuel mobilization and storage; the effect of meal pattern, diet induced

thermogenesis, exercise and energy metabolism; thyroid function and thermogenesis; the factors affecting appetite, hunger, and diet selection; behavioral techniques for weight loss; and behavioral and genetic correlates of obesity.

The U.S. Malnutrition Panel of the U.S.-Japan Cooperative Medical Sciences Program continues to be administered by NIADDK. The nutrition research fostered under the program investigates protein calorie malnutrition, iron and vitamin A deficiencies. Solutions to these problems are primarily targeted to the undernourished populations of Asia and other areas of the Pacific Basin.

The NIADDK supports five Clinical Nutrition Research Units, namely, those located at the University of Chicago, University of Wisconsin, Vanderbilt University, the Medical College of Georgia, and Columbia University. The CNRU mechanism is stimulating progress in a multidisciplinary approach to clinical nutrition research, enhancing patient care, strengthening training environments in nutrition for medical students and other health professionals, and generating nutrition information for the public.

The National Institute of Neurological and Communicative Disorders and Stroke supports research on the dietary and metabolic factors that contribute to the growth, development, and overall health of the somatic (central and peripheral) and autonomic nervous systems. Nutrition studies in molecular biology, hemodynamics and immunochemistry of the nervous system form the basis of many clinical investigations. Attempts to clarify the two-way interaction between nutrient intake and function of the central nervous system include studies on the effects of protein-calorie malnutrition and vitamin deficiencies on central nervous system metabolism and fetal development; the mechanism of nutrient transport and their metabolic products across the blood-brain and blood cerebrospinal fluid barriers; the metabolic effects of nutrients on inborn errors of metabolism associated with neurological impairment; the influence of nutrients on the onset or progress of other neurological disorders; the neural control of ingestive and drinking behaviors; and the effect on appetite of the interaction between gustatory sense and olfaction. Basic and clinical studies examine the neurophysiological mechanisms of taste and their possible relationship to diabetes, obesity, kidney disease and radiation-induced illnesses. The effect of diet on hormonal and metabolic regulations of energy expenditures, ingestive behavior, and weight loss is also under investigation.

Studies are carried out on the relationship between dietary habits of various primitive cultures and the incidence of slow virus infections, such as Creutzfeldt-Jakob disease, Alzheimer's disease and amyotrophic lateral sclerosis; on abnormalities in gastrointestinal absorption of hereditary sensory neuropathy; and in the use of high fat diets in the treatment and control of seizures in children.

The National Institute of Allergy and Infectious Diseases promotes and supports research in the broad field of nutrition, infection, and immunity. Investigations focus on the mechanisms of food allergies in relation to the immune response to ingested antigens; the modulating effect of

specific nutrients, such as amino acids, vitamins, minerals, and fatty acids on basic immune functions; the modulating effect of specific nutrients, particularly iron, on microbial virulence; the effect of malnutrition on resistance to infections, especially infectious diarrhea; the role of breast milk in defense against enteric infections and the effect of infections on nutritional status; and the interaction between nutrition and infection in the American hospitals. Epidemiological studies examine malnutrition and hospital acquired infections in different clinical situations. Other research is concerned with the effects of parenteral and enteral nutrition support of the patient on immune function and hospital infections.

The National Institute of General Medical Sciences supports research directed to the discovery of better ways to prevent death from injury, mitigate pain, speed recovery of patients, and lessen the extent of disabilities caused by injuries. A better understanding is sought of the total body response to trauma, including burns. Studies include the biochemical and physiological changes induced by trauma, and the fundamental aspects of wound healing and biological repair. Emphasis is also given to research on the treatment of post-traumatic infections, nutritional requirements of burn victims, and rehabilitation of injured patients. The NIGMS trauma and burn program supports research related to nutrition in the following areas: nutritional aspects of severe trauma and sepsis, new concepts in parenteral protein sparing therapy, branched chain amino acid feeding during injury, and cellular response in shock.

The National Institute of Child Health and Human Development extramural research program focuses on the continuum of human development, from conception through infancy, childhood, and adolescence. The program emphasizes preventive approaches to nutrition-related conditions and stresses health promotion as well as disease prevention. Much of the research is multidisciplinary in nature and involves genetic, biochemical, developmental, anthropometric, behavioral, and cultural aspects of nutrition.

The NICHD has a strong interest in the area of maternal and infant nutrition and in elucidating the roles played by diet in infant development. Research interests focus on the nutrient requirements of normal, premature, and growth retarded infants, as well as on the composition of human milk, cow's milk and synthetic formulas in relation to optimal infant nutrition. In some of this work, the interest centers on metabolic processes in neonatal adaptation, and on the role played by essential nutrients and other components of human milk in optimizing early development. Studies on human milk and colostrum emphasize the conveyance of passive immunity to the young infant; the roles played by specific components of milk in stimulating cerebral and gastrointestinal development; and the effect of maternal factors such as age, parity, nutritional status and duration of lactation on breast milk composition. A major contract is designed to develop human milk banking technologies for collection, storage, processing, and distribution of human milk and colostrum; the goal is to discover ways to preserve the labile nutritional and immunological components of these complex fluids during processing and storage. A 3-year study will evaluate the physical growth, immunological development, and gastrointestinal function of low-birth-weight infants fed human milk versus formula.

Studies in nutrition and child development emphasize nutrition as a potentiating factor in cerebral and somatic development. Research interests include the relationship of protein intake and trace metals to cerebral growth and function; the effect of nutritional deficits and excesses on physical growth and maturation; and the effect of non-nutritive food components, such as toxins, allergens, and contaminants, on the growth, development and health of children.

In order to assess optimum development in children, adequate nutrition should be provided to them in utero. Research continues to examine the complex relationship between the mother and her fetus in terms of nutrient transfer across the placenta, and to ascertain the effects of excessive or deficient amounts of certain nutrients on the morphologic and endocrine development of the fetus.

Most studies on nutritional aspects of developmental gastroenterology consist of basic research on cellular differentiation in relation to the functional development of the gastrointestinal tract. Human milk appears to provide specific components that stimulate functional development of the newborn's intestinal tract as well as digestive enzymes, such as lipases, which the infant is unable to produce in sufficient quantities. Studies are also progressing on digestive and absorptive disorders during infancy, particularly intractable diarrhea.

Research on dietary therapy of inborn errors of metabolism looks at abnormal metabolism of nutrient substrates. Included are investigations of the biochemistry and genetics of inborn errors which are, or may prove to be, treatable with diet. Many inborn errors of metabolism cause mental retardation or other disabilities of the central nervous system. Clinical research has shown that some of these diseases are amenable to nutritional management, as are a number of inherited metabolic diseases not associated with mental subnormality, such as lactase deficiency, cystic fibrosis, and some hereditary anemias. In most inborn errors of metabolism, the mechanisms by which aberrant levels of metabolic intermediates interfere with cerebral function remain unknown; neurochemical research in animal models, e.g., experimental phenylketonuria and galactosemia, is being supported to answer this central question.

Research on cultural and behavioral determinants of nutritional individuality includes studies of habits, taste and olfaction; food avoidances; behavior modification of dietary intakes; and projects on children's conceptualization of food and on the influence of television commercials on children's food preferences. Research on nutritional antecedents of adult disease focuses primarily on factors in the development of obesity in infancy, childhood, and adolescence. Behavioral, neurochemical, genetic and hormonal factors involved in obesity are under investigation; the psychosocial and nutritional aspects of both adolescent obesity and anorexia nervosa are being studied. Studies also examine nutrition's role in diabetes in pregnancy and among infants of diabetic mothers.

Other NICHD research emphasizes the development of new methods for assessing nutritional status, particularly during infancy, adolescence, pregnancy, and lactation. New noninvasive methods are being developed to

measure serum ferritin, serum vitamin E, lactose absorption and body composition. Mass spectrometric studies use stable isotopes of calcium, lecithin, and amino acids, while X-ray fluorescence spectroscopy and atomic absorption spectrophotometry are also being used.

Studies also investigate the effects of nutritional alterations on gonadotrophin secretion, ovarian function and fertility. Research emphasizes the role of vitamins and minerals in sensitive reproductive processes (such as spermatogenesis), and the effects of oral contraceptives on the metabolism of folic acid, pyridoxine, and ascorbic acid. The reproductive consequences of low protein diets as reflected in gonadotropin production, fertility, and lactation are also under investigation. Other NICHD researchers are looking at the augmented nutrient demands caused by the growth spurt and the onset of puberty.

The National Eye Institute supports research on the role of overall nutrition as well as specific nutrients, such as vitamins A and E, protein, copper, and zinc, on normal ocular and visual development, health and function. Studies also examine the association between nutritional imbalances and eye and vision disorders, such as cataracts, retrolental fibroplasia, and childhood blindness.

The role of vitamin A in the visual process, particularly in the generation and recycling of rhodopsin, is an important research area since vitamin A deficiency is the leading cause of blindness in children living in the developing world. Investigators are studying the interaction in ocular tissue of vitamin A with other nutrients, such as vitamin E and zinc; the role of binding proteins for retinoids in ocular tissue compartments; and the factors that modify their synthesis and metabolism. Other studies are under way to examine how differences in protein and lipid composition alter ocular membrane structure and function. Of particular interest are alterations in membrane phospholipids that influence intercellular transport of calcium, copper and zinc and its consequential effects on the visual process and the development of retinopathies.

Research findings have shown that pharmacological doses of specific nutrients, particularly vitamin E, may protect ocular tissue with various retinopathies. For example, vitamin E's role in reducing the incidence and severity of retrolental fibroplasia in the premature infant and in protecting the cytotoxic effects of accumulated natural or induced oxidants is being investigated.

Studies are under way on the effect of specific nutrient deficiencies, such as vitamins A, E, ascorbic acid and riboflavin, tryptophan and taurine, zinc, selenium, and copper on the eye. Imbalances in these nutrients are being considered as possible risk factors for cataract development. Other investigations examine the visual system's ability to recover from trauma in terms of the effect of specific nutrients on the ocular immune responses.

The National Institute of Environmental Health Sciences supports research on the biological risks and toxic adverse effects of environmental agents such as food-borne contaminants and additives on biological systems.

Food toxicology research examines naturally occurring products, such as those present as food plant components or mycotoxins (aflatoxins), as well as chemical agents intentionally introduced to foods as additives or unintentionally as environmental contaminants. For example, the effects of heavy metal intake on the metabolism and balance of essential elements are being examined. These studies hope to clarify how natural food products such as mycotoxins or their metabolites are generated in the body; the specific mechanisms of food toxicity; the interactions of food-borne contaminants with other environmental agents that increase or decrease toxicity; and the health risks associated with exposure to food contaminants.

Other studies investigate contaminants resulting from food storage generated under suboptimal storage conditions. Food processing hazards such as nitrites, nitrates and other additives are being studied to learn how they are altered in the foodstuff and how they are transformed by biological systems.

Food toxicants and toxic alterations of absorption, metabolic and excretory functions of the gastrointestinal tract are being investigated not only in terms of their role as biological stressors, but also to understand how the toxicant interacts with other environmental contaminants. Additional studies seek to determine toxic changes generated in the enterohepatic, biliary and renal systems by environmental contaminants and the alteration of these systems to prevent biological insults through decreased absorption and enhanced secretion.

The National Institute on Aging supports basic and clinical investigations on nutrition's role in the aging process. For example, studies are under way on the effects of food restriction on increased life span, and the effect of nutritional status on immune function and in the structure and function of several tissues, including adipose, hepatic, brain, muscular, skeletal, and vascular tissues. Research continues to examine the normal nutrient requirements of the elderly, as well as when altered by disease or chronic drug regimens.

Other research involves the role of specific dietary components in various age or disease-related processes common in the elderly. Studies on the effects that various age-related physiological changes may have on nutritional status focus on changes in renal physiology, intestinal physiology, taste and smell, salivary secretions, and dentition. Such physiological changes affect food intake and the digestion and absorption of necessary nutrients. Also under investigation is the relationship between nutritional status and subsequent morbidity and mortality among the elderly in terms of such diseases as cancer, coronary heart disease, stroke, osteoporosis, etc. For example, studies consider the role of vitamin D in calcium transport and subsequent bone turnover in postmenopausal women, as well as the effect of protein malnutrition on reduced immune function often found in the elderly.

The Division of Research Resources provides many of the basic resources needed to perform clinical nutrition research. In FY 1982, DRR supported 75 General Clinical Research Centers in the U.S. The research beds, laboratories, and professional nursing and dietary personnel that

comprise each center are essential to clinical investigation in nutrition. These centers conduct clinical nutrition studies on atherosclerosis, cancer, diabetes, environmental health factors, hyperlipidemias, obesity, parenteral nutrition, and vitamins. In all, the dietary support personnel working in these centers number 235 full-time equivalent, while 879 dietetic personnel are trained there annually. Several of the 40 full-time equivalent clinical associate physicians are directly involved in clinical nutrition research. The team approach in clinical investigation at the centers allows the basic scientist, clinician, dietitian, and nurse to interact in developing systematic methods for nutrition research. Research in nutrition is also enhanced by the four other DRR programs that serve health researchers throughout the country: Biotechnology Resources, Laboratory Animal Resources, Biomedical Research Support, and Minority Biomedical Support.

In summary, the Institutes with mandates in categorical diseases support nutrition research programs in their areas of responsibility in both the prevention and the treatment of disease; namely, NCI on diet and cancer; NHLBI on diet and heart, lung and blood disorders; NIDR on nutrition and dental caries; NIGMS on nutrition and trauma including burns; and NEI on nutrition and various eye disorders. NIADDK, NICHD, and NIA support nutrition research particularly related to nutrient requirements relevant to the different stages of the life cycle and specific metabolic and genetic diseases. NINCDS supports research on nutrient intake and metabolic changes as these affect the nervous system in health (growth and development) and disease; NIAID on the role of nutrition on infection and immune system function; and NIEHS on the effect of environmental agents such as food contaminants and additives on biological systems. Through studies in biochemistry, physiology, and cell biology, NIH supported research aims to elucidate fundamental mechanisms in order to synthesize the results into practical information on nutrition and diet that will assist the individual to develop normally, and to live as long and as healthy a life as possible.

Manpower Development

Manpower development in nutrition research is enhanced through research career development awards and new investigator research awards. The total obligation for these programs was \$3,261,000 in FY 1982.

Research Career Development Awards (RCDA's) in nutrition for FY 1982 included 34 "Modified Research Career Development Awards" (K04), 4 "Research Career Awards" (K06), 15 "Academic/Teacher Awards" (K07), and 5 "Clinical Investigator Awards" (K08). These 58 awards were awarded by NCI, NEI, NHLBI, NIA, NIADDK, NIAID, NICHD, NIDR and NIGMS for a total obligation of \$1,361,000.

"Modified Research Career Development Awards" foster the development of young scientists with outstanding research potential for careers of independent research in the sciences related to health.

"Research Career Awards" enable institutions to finance positions favorable to the intellectual growth and research productivity of established investigators of high competence for the duration of their careers.

"Academic/Teacher Awards" create and encourage a stimulating approach to disease curricula that will attract high-quality students, foster academic career development of promising young teacher-investigators, develop and implement excellent multidisciplinary curricula through an interchange of ideas, and enable the grantee institution to strengthen its existing teaching program. The academic and teacher investigator awards are not used by all of the B/I/D's.

"Clinical Investigator Awards" provide the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members who will pursue research aspects of categorical areas applicable to the awarding unit, and aid in filling the important academic faculty gap in these shortage areas within health professional institutions of the country.

Recipients of these awards conduct nutrition research in the areas of basic metabolism, human growth and development, nutrition and cancer, and cardiovascular disease.

Metabolic studies include research on: metabolic and endocrine aspects of obesity; regulation of human gastric responses to meals; hypothalamic control of body weight and feeding; evaluations of dietary alterations and treatments; epidemiology of digestive diseases; neural and humoral control of mucosal transport; study of nutritional and hemolytic anemias; gastrointestinal digestion and absorption of fats; metabolic role of cobalamin and folate; folate supply and utilization; glycerol-3-phosphate dehydrogenase and egg yolk avidin; metabolic effects of burn injury and sepsis; nutrition and drug metabolism in man; methods and techniques for localizing and quantifying ions and trace elements in soft biological tissues for application to the evaluation of retinopathies; vitamin A transformations in the light and dark adapted photoreceptor cell, i.e., regulation of 11-cis-retinaldehydrogenase; the intracellular transport role of binding proteins; the physiological role of esterified vitamin A in photoreceptor cells, and the interaction between photoreceptors and pigment epithelial cells; resonance raman microscopy of visual photoreceptors; and the biochemistry of oral tissues, secretions and diseases.

Studies on human growth and development include research on: the pattern of development of fatty acid oxidation capacity by the neonatal liver that would help to standardize techniques for radiological binding, necessary to measure beta-adrenergic receptors in purified liver plasma membranes; nutrition and development of adipose tissue, i.e., lipoprotein lipase activity related to feeding behavior; the role of glucose production in the developmental maturation of neonatal carbohydrate homeostasis; developmental aspects of renal transport and experimental models of Fanconi syndrome; maturational and adaptive changes in intestinal carbohydrate absorptive capacity during the postnatal period with emphasis on the effects of breast feeding, defined nutrient formulas, and gastrointestinal dysfunction; the composition of weight loss and weight gain in human subjects; the development of an instrument to measure the electrolyte content in infants; the appropriate forms and levels of vitamin-D supplements for pre-term and term infants; dietary habits during childhood and etiology of breast cancer or other diseases in later years; and pathogenic mechanisms

for impaired leukocyte mobility in pediatric patients having severe protein-calorie malnutrition.

Investigations on nutrition and cancer include research on: the biosynthesis of mammalian glycoproteins, lipids and membrane structures of leukemic leukocytes; thymidine transport in normal and leukemic lymphocytes; asparagine biosynthesis in normal and tumor cells; hexosaminidase levels and diet; human mucosal structure and function; and normal and tumor cell regulation of folate polyglutamate synthesis.

In the area of cardiovascular disease, research includes: the regulation of cholesterol metabolism in cultured cells; coronary risk, family life-style and behavior change; outcomes of behavioral programs for chronic obstructive pulmonary disease and diabetes; the effects of diet on blood pressure; lung hyperoxia; and the effects of nutrition, age, and drugs on cardiovascular disease.

New Investigator Research Awards (NIRA) are used also by the NIH as a mechanism for manpower development in nutrition. The NIRA (R23) encourages new investigators (including those who have interrupted early promising research careers) in basic or clinical science disciplines to develop their research activities within the program interests at NIH. This special grant supported program provides research grant funds to help bridge the transition from training status to that of established investigator. In FY 1982, 60 new investigator research awards were awarded for a total obligation of \$1,900,000 supported by all of the Institutes except NIEHS.

The areas under study by the 60 recipients of these awards include basic metabolism in growth and development, fat metabolism and obesity, vitamin and trace mineral metabolism, immune function, eye disorders, trauma, hypertension and cardiovascular disease, and cancer. Examples of studies in each of these areas are as follows:

- ° basic metabolism in growth and development - intestinal membrane structure and functional development; hepatic regulation of leucine metabolism; the effects of malnutrition during pregnancy or lactation; developmental aspects of hepatic bile and transport in human infants and developing rats; the effect of nutrition on neonatal intestinal metabolism, specifically those factors controlling substrate oxidation in rat intestine during suckling, weaning and postweaning periods; the effects of diet on attention span, activity level, anxiety, hyperactivity, aggression and tantrums in 4-year-old children.
- ° fat metabolism and obesity - effects of dietary intervention on weight loss in obese (FA/FA) rats; the role of beta endorphins on feeding and obesity; the effect of weight loss and exercise on lipoprotein lipase; opioid peptides' effects on food intake, selection and obesity; biliary tract motility in the fasting and fed state; the regulation of experimental obesity via the sympathetic adrenal axis; regulation of fat and protein synthesis; regulation of cholesterol esterification in the intestine; lipid

esterification in the liver and mammary gland; molecular dynamics of lipoprotein lipase; the regulation of enzymes in triacylglycerol metabolism; phospholipid metabolism in plasma lipoproteins; kinetics of lipolysis in the plasma of normal and hyperlipemic individuals; serum lipoprotein levels of rabbits fed atherogenic diets; the effects of thermal environment on growth and energy balance in premature infants hospitalized in neonatal intensive care units; the effect of energy intake on the rate and composition of weight gain in premature infants; aerobic training and efficiency of energy utilization; and neurobehavioral analysis of glucagon on satiety.

- ° vitamin and trace mineral metabolism - dietary regulation of vitamin D in health and uremia; the effects of changes in vitamin D metabolism during pregnancy on fetal growth and skeletal development; factors that influence the choline and methionine content in milk and tissue choline concentrations; the influence of trace metals on dental health; trace mineral bioavailability and metabolism studies; metabolism of dietary sulfur in altered liver function; mechanisms of chloride transport by rabbit colon; and biological utilization of molybdenum.
- ° immune function - the effect of *Schistosoma hematobium* infection on nutritional status, i.e., anemia, growth and physical fitness of school-age children in Kenya and the benefits of a safe and inexpensive oral drug on nutritional status; mitogen and antigen induced production of two lymphokines in human milk; the transfer of cellular immunity to tuberculin antigen via breast milk to the nursing neonate; the investigation of reduced host defense and nutritional status in the elderly determined by complete nutritional, hematological and immunological assessments; intestinal membrane structure and functional development; and the immunology of ocular surface cells of mesenchymal origin that possess characteristics of macrophages in terms of their response to corneal irritants and vitamin A deficiency.
- ° eye disorders - the study of cytosol retinoid binding proteins (from the retina, pigment epithelium, testes, and liver of several species of animals) in order to understand their molecular structure, functions in the eye, and effect of deficiencies on altered retinol binding specificity and affinity; the role of excitatory amino acids in the visual process vis-a-vis the photoreceptors and bipolar cell transmitters in the retina of fish, amphibians and mammals; the corneal uptake and metabolism of topically applied retinoids with respect to their efficacy in the treatment of xerophthalmia and promotion of corneal wound healing; the role of phosphorylation of the vitamin A pigment rhodopsin in vision and the role of calcium levels in regulating the phosphorylation process; and epidermal lipids and disorders of keratinization.
- ° trauma - hypermetabolism after severe head injury in children.

- ° hypertension and cardiovascular disease - blood pressure levels and the role of common residence and network dynamics as a diagnostic unit; the measurement of cardiovascular parameters during maximal exercise (i.e., oxygen consumption, cardiac output, stroke volume, heart rate, and O₂ extraction), as well as the measurement of pulmonary function, serum lipids, body composition, glucose tolerance, and echocardiographic left ventricular function in young (<25 years) and older (>50 years) athletes matched on the basis of training and performance; the effect of exercise training on 60-year-old sedentary individuals in terms of O₂ uptake, glucose tolerance, plasma insulin levels, and the development of coronary artery disease.
- ° cancer - pineal-endocrine-dietary influence on mammary tumors; relaxation training to reduce aversion to chemotherapy; sodium ions and mitogenic signaling; lymphocyte carcinogen metabolism in acute leukemia; growth and differentiation of mast cells and T cells; oxygen radicals and anticancer quinones; screening for inhibitors of N-nitrosamine carcinogenesis.

Program Development

A major responsibility of the NCC is to identify areas for further research and bring them to the attention of the scientific community through the development and publication of program announcements, requests for applications, and requests for proposals.

A PA is a formal statement of an NIH extramural research activity or of the initiation of a new or modified mechanism of support. It may describe new or modified program interests, or simply be a reminder of continuing interest.

A RFA is a formal statement which (a) invites grant applications in a well-defined scientific area to accomplish specific program purposes, (b) generally identifies only one application receipt date, and (c) indicates whether or not funds have been set aside for the competition and, if so, the amount of funds and/or the expected number of awards to be made. A RFA may be reissued as necessary.

PA's and RFA's often lead to the receipt and funding of many applications. For instance, 35 grant applications were received in response to the PA on "Adolescence Research."

An RFP is the Government's invitation to prospective offerors to submit a contract proposal based on the terms and conditions set forth in the RFP by the statement of work that describes the nature of intended procurement. The number of contracts awarded as a result of an RFP is smaller.

Table V lists the 15 PA's, RFA's, and RFP's in nutrition published in FY 1982, with the origin and date of each announcement, the type of announcement, and its title. A brief description of each announcement follows the table. Included in the table are 7 PA's, 7 RFA's, and 1 RFP.

TABLE V

PA's, RFA's, and RFP's in Nutrition Research and Training
Published In The NIH Guide For Grants and Contracts, FY 1982

ISSUED BY	DATE	TYPE	TITLE
NIADDK NICHD NIAID	11/6/81	PA	"Research Grant Support in Nutrition: Environmental and Host Factors Affecting Nutritional Requirements"
NICHD	11/16/81 (9/17/82)	RFP	"Long-term Effects on Infants of Hypochloremic Metabolic Alkalosis Resulting From Infant Formulas Deficient in Chloride" (Amendment of Solicitation)
NICHD	2/26/82	PA	"Successive Small-For-Gestational Age Births: A Longitudinal Study of Fetal Growth and Perinatal Outcome"
NHLBI NIA, NIAID, NIADDK, NICHD, NIGMS	2/26/82	PA	"Studies on Nutritional Support of the Patient"
NCI	3/26/82	RFA	"The Role of Natural Inhibitors in the Prevention of Cancer"
NIDR	3/26/82	PA	"Epidemiology of Oral Diseases in Minorities"
NIAID	4/23/82	RFA	"Asthma and Allergic Disease Centers"
NICHD	4/23/82	PA	"Adolescence Research"
NIAID	4/23/82	RFA	"Centers for Interdisciplinary Research In Immunologic Diseases"
NHLBI	4/23/82	PA	"Dietary Sodium and Its Role in the Prevention and Management of Hypertension"
NIDR	4/30/82	PA	"Clinical Trial of the Effect of Prenatal Fluoride Supplements in Preventing Dental Caries"
NIDR	7/16/82	RFA	"Fluoride and the Prevention of Root Surface Caries"
NCI	8/13/82	RFA	"'Accuracy' of Questionnaire Derived Historic Dietary Information"
NCI	8/13/82	RFA	"Epidemiologic Studies of Rare Tumors"
NCI	8/13/82	RFA	"Biochemical Epidemiology"

The PA, "Research Grant Support in Nutrition: Environmental and Host Factors Affecting Nutritional Requirements," issued by NIADDK, NICHD, and NIAID, encourages studies to quantitate the dietary requirements for the essential nutrients that may be affected by age, state of human development (from fetal life to adulthood), sex, and occupation, and are known to be limiting in populations living under various ecological conditions. The U.S. Malnutrition Panel of the U.S.-Japan Cooperative Medical Sciences program has recommended that priority attention be given to studies in research areas that include: the effect of chronic infection, diarrheal disease and/or parasitism on digestion and absorption of specific nutrients or diet components; the effect of nutritional and non-nutritional dietary components on the bioavailability (absorption and utilization) of limiting essential nutrients; the determination of the functional significance of nutrients considered to be potentially limiting under a variety of dietary and ecological conditions. Dietary components of special interest include energy, protein, essential amino acids, iron, zinc, vitamin A, and B₁₂. Collaborative research between U.S. investigators and investigators in Asia, or in other countries with nutritional problems similar to those in Asian countries, is particularly encouraged.

The RFP, "Long-term Effects on Infants of Hypochloremic Metabolic Alkalosis Resulting from Infant Formulas Deficient in Chloride," issued by NICHD, sought proposals for a retrospective cohort study of children with a documented history of exposure to chloride deficient Neo-Mull-Soy or Cho-Free infant formulas during 1979 that resulted in metabolic alkalosis. Specific objectives of the study are: 1) to review the discharge diagnoses of metabolic alkalosis from hospitals for 1979 using the CPHA/PAS, CHAMP, and other similar sources in order to identify children who suffered from metabolic alkalosis while exposed to the chloride deficient Neo-Mull-Soy or Cho-Free diet; 2) to identify three control groups: siblings of the exposed children; children on a soy bean based formula other than Neo-Mull-Soy or Cho-Free matched by race, sex, age, and parental socioeconomic status; and another matched group of children who were breast fed or on a cow's milk based formula; 3) to obtain information about the past and current health and development status of the children, and their status before and after exposure to the chloride deficient formula; and 4) to follow the children at ages 5 to 6 and 9 to 10 years in order to obtain data on physical growth, gross motor development, and on any major deviations, including neurological impairment and mental retardation. Schools will also be contacted to obtain data regarding the child's school performance, class standing, and other information aimed at identifying serious impairment in learning ability. This RFP resulted from the Infant Formula Act of 1980 which directs that "the Secretary of Health and Human Services shall conduct a study to determine the long-term effects on infants of hypochloremic metabolic alkalosis resulting from infant formulas deficient in chloride. The Secretary shall report the results of this study to Congress."

The PA, "Successive Small-For-Gestational Age Births: A Longitudinal Study of Fetal Growth and Perinatal Outcome," issued by NICHD, is seeking sources capable of performing a study of pregnant women at risk

of delivering small-for-gestational age births (defined as birth weight less than 10th percentile for gestational age). The purpose of the study is to identify epidemiological risk factors which predispose mothers to have: a) repeated small-for-gestational age births and b) unexpected nonrepeated small-for-gestational age births. The study will include interviews for ascertaining nutritional and lifestyle factors from mothers in the second and third trimester; fetal growth monitoring with diagnostic ultrasound measurements at regularly specified intervals; and the collection of appropriate and uniform medical data, prenatally, perinatally and throughout the first year of life.

The PA, "Studies on Nutritional Support of the Patient," issued jointly by NHLBI, NIA, NIAID, NIADDK, NICHD, and NIGMS seeks applications on the basic and clinical research aspects of the nutritional support of patients needed in order to better understand when to institute parenteral or enteral nutrition. Results from the research will help to maximize therapy and avoid its indiscriminate use which increases medical costs and patient risk and discomfort. Apart from its obvious therapeutic importance, parenteral and enteral nutrition provides a powerful research tool to probe and manipulate host metabolism and physiology, particularly in animal models. Research applications are being sought in the following areas: the impact of nutritional status on defense functions in the adult and developing lung (NHLBI); the specification of the nutritional requirements of elderly patients and subsequently the enteral and parenteral nutritional support in elderly patients in acute and long-term care facilities; the assessment of the efficacy of current enteral and parenteral therapies for elderly patients (NIA); the interaction of nutrition, infection, and immunity with precise mechanisms mediating changes in immunocompetence and resistance to infection clarified, and the effects of infectious agents on nutrient metabolism elucidated (NIAID); the nutritional support of the patient as it affects the nutritional status of the whole individual (such as in cases of obesity, chronic renal failure, end-stage renal disease, anorexia nervosa and surgical trauma); nutritional status assessment methodologies; the effect of disease on nutritional requirements and the effect of nutrient intake levels on the course of specific diseases or conditions (e.g. organocentric or disease oriented studies that primarily involve investigations related to kidney, liver, pancreas, bone and digestive diseases) (NIADDK); the nutritional support of the low-birth-weight infant and the nutritional management of certain disease states of infancy and childhood in terms of the safety and efficacy of intravenous administration of nutrients (NICHD); and studies on the metabolic and nutritional response to accidental injury, including burns (NIGMS).

The RFA, "The Role of Natural Inhibitors in the Prevention of Cancer," issued by NCI, seeks applications for studies to: 1) elucidate further the protective effects of several natural inhibitors in reducing the incidence of various site specific cancers; and 2) lead to a greater understanding of the extent, or action, of several natural inhibitors in the possible cancer prevention process in humans. Natural inhibitors associated with the inhibition of carcinogenesis or with reduced cancer incidence in epidemiological investigations include vitamin C, vitamin A or its analogs, beta carotene, selenium and alpha tocopherol. The

following types of studies are considered appropriate research approaches to this investigation: Case control studies of cancer patients and matched controls on the relationship of designated inhibitors with cancer incidence; cohort studies of populations that have consumed varying levels of the inhibitors; studies to examine the long-term consequences of chronic intake of various compounds in order to monitor possible adverse health effects; and risk reduction clinical trials with designated natural inhibitors administered to high risk populations free of neoplasia, or with identified precursory or precancerous lesions.

The PA, "Epidemiology of Oral Diseases in Minorities," issued by NIDR, encourages applications for the support of epidemiological research related to oral health problems of racial and ethnic minority groups. Research proposed may be directed toward the identification of the patterns of occurrence, the factors and conditions, including behavioral factors, responsible for or contributing to oral health problems, such as dental caries (in terms of the prevalence of both coronal and root caries in different age groups); periodontal diseases (with studies using new methodologies for objective measurement of disease activity); congenital craniofacial anomalies (including cleft palate); and oral malignancies; other soft tissue diseases; and nutritional deficiencies with oral manifestation.

The RFA, "Asthma and Allergic Disease Centers," issued by NIAID, seeks new and renewal applications for the development of Asthma and Allergic Disease Centers (AADC). The fundamental objective of the AADC program is "acceleration of the application of emerging knowledge on the immune system and from relevant biomedical sciences to clinical investigations concerned with asthma, allergic diseases, and hypersensitivity disorders." The requisite factors sought within a participating institution are quality research in (1) basic science(s); (2) clinical investigation supported by adequate clinical facilities, and staff expertise in diagnosis and management of asthmatic and allergic patients; and (3) access to an appropriate patient population(s) within a suitable academic setting designed to favor multidisciplinary interaction. Areas of study within the provision of this program may include those relevant to asthma and its multifactorial aspects; atopic diseases (e.g. allergic rhinitis, urticaria); pathological expressions, pathophysiological mechanisms, and genetic factors of allergic disease and inflammation; identification, isolation and characterization of etiologic agents of allergy (e.g. drugs, foods, airborne allergens); immune mechanisms and agents of immediate hypersensitivity; and immunopharmacology, immunotherapy and the development of specific pharmacological agents designed for the prevention and treatment of asthma and other allergic diseases.

The PA, "Adolescence Research," issued by NICHD, seeks applications to support fundamental research related to biomedical and behavioral aspects of adolescence through two extramural research centers: The Center for Research for Mothers and Children (CRMC), and the Center for Population Research. One branch of the CRMC, the Clinical Nutrition and Early Development Branch, is concerned with the special nutritional requirements of the adolescent and those factors related to food choice and obesity. Since the assessment of nutritional status of adolescents is particularly

difficult because food patterns are often erratic, the following areas are of research interest: definition of nutrient requirements associated with the adolescent growth spurt and the onset of puberty; the development of new methods and the validation of existing methods for assessing nutritional status that are applicable to adolescence; elucidation of the cognitive, emotional and social processes involved in food choices by adolescents; investigation of the contribution of exercise and energy balance to obesity during adolescence, as well as the potential and undesirable health effects of weight reduction regimens in the obese young adolescent still undergoing physiologic maturation; and exploration of the psychological and cultural determinants of adolescent obesity through studies of techniques for modifying eating behavior and for stimulating obese adolescents to lead more active, healthful lifestyles.

The RFA, "Centers for Interdisciplinary Research in Immunologic Diseases," issued by NIAID, seeks grant applications for the participation in the ongoing program of the Centers for Interdisciplinary Research in Immunologic Diseases (CIRID). The fundamental objectives of the CIRID program are to accelerate the application of emerging knowledge on the immune system and from relevant biomedical sciences to clinical investigations concerned with asthma, allergic diseases, hypersensitivity disorders, and immunologically mediated disorders. Suitable subjects for study within the provision of this program include immunologic disorders; asthma and its multifactorial aspect and atopic diseases (e.g. allergic, rhinitis, urticaria); identification, isolation and characterization of etiologic agents of allergy (e.g. drugs, chemicals, foods, airborne allergens); pathologic expressions, pathophysiologic mechanisms and genetic factors of allergic disease and allergic inflammation. In addition to developing broad interdisciplinary research programs in immunology, the centers will be expected to carry out other educational or community activities.

The PA, "Dietary Sodium and Its Role in the Prevention and Management of Hypertension," issued by NHLBI, seeks applications for a broad range of investigations that include physiological, clinical, preventive, and therapeutic research, on the role of dietary sodium in hypertension and the prevention of hypertension. Examples of the research studies needed are as follows: the interrelationship of sodium and weight; sodium sensitivity; salt appetite; and methodology for determining sodium intake in humans. Investigations that take into account other dietary factors, caloric intake, and energy expenditure are encouraged.

The PA, "Clinical Trial of the Effect of Prenatal Fluoride Supplements in Preventing Dental Caries," issued by NIDR, is an attempt to determine, identify, and secure a potential study population of approximately 1,200 pregnant women who reside in areas with less than 0.3 p.p.m. fluoride in the drinking water, in order to conduct a clinical trial of the efficacy of prenatal fluoride supplements in preventing caries in primary dentition. Caries prevalence in children whose mothers received daily fluoride supplements (1 mg F per day) during pregnancy will be compared with that of children whose mothers received placebos. Children of both groups will receive daily fluoride supplements from birth until the age of 5

years. Dental caries examinations will be conducted when the children are 3 and 5 years of age.

The RFA, "Fluoride and the Prevention of Root Surface Caries," issued by NIDR solicited applications to investigate the effect of fluoride on the mineralization, demineralization and remineralization of artificially or naturally induced incipient lesions on root surfaces and to elucidate the anticariogenic effects of fluoride on the bacteria associated with this process. Epidemiological studies have shown that the incidence and prevalence of root surface caries is increasing in the U.S. population and that it is becoming a serious public health problem. Although the etiology of root caries is not fully understood, diet, salivary properties and rate or flow of saliva and bacterial flora in the mouth are believed to play an important role in the disease process. Evidence suggests that fluoride may be effective against root surface decay; i.e., on the basis of the effectiveness of fluoride in preventing enamel surface lesions, the variety of oral pathogens sensitive to fluoride, the histological and environmental similarities of enamel and cementum, as well as the apparent similarities in the caries process in both tissues.

The RFA, "'Accuracy' of Questionnaire Derived Historic Dietary Information," issued by NCI, seeks applications for studies designed to investigate the "accuracy" and reproducibility of historical dietary information by comparing current information obtained by questioning individuals or their surrogates with actual records (data reflecting past dietary intake) of the same individual recorded at some earlier point in time. Since nutrition has received significant emphasis as a potential etiologic or modulating factor in human carcinogenesis, it has become increasingly important to assess the degree to which dietary histories can be relied upon as substitutes for hard data on past food consumption or changes in dietary patterns. The primary focus is on the value of historical dietary information as a predictor of cancer risk since the cancer epidemiologist needs information on how well historical dietary data separates individuals into low, middle or high consumers of a specific dietary component or food group. It is also of interest to determine the "accuracy" of recall information from surrogate respondents, since this procedure is necessary when conducting cancer epidemiology studies where the individual of concern is deceased or unable to respond adequately. Additional variables other than elapsed time which might be investigated include the age and sex of subjects, educational level, health status, complexity of questioning, dietary variability, and the effects of "out of home" food consumption. The usefulness of special techniques to improve recall, validity of the original dietary data, its generalizability and/or the availability of laboratory markers of previous exposure should be assessed.

The RFA, "Epidemiologic Studies of Rare Tumors," issued by NCI, seeks applications for studies aimed at the elucidation of causal factors in the development of rare cancers such as malignancies of the thyroid, anus, oral canal, and anorectum; soft tissues, including heart, bone and joints; male breast; penis; and salivary gland tumors. Potential etiologic factors that could be addressed include occupational/environmental exposure,

genetic/familial factors, diet, drug use (therapeutic and other), cigarette smoking, behavioral factors, etc. These studies are to generate causative/etiologic hypotheses to provide clues of association, and/or to develop improved research design/methodology for the study of rare cancers. They also can provide the basis for more extended research designed to provide information on the etiology and natural history of specific rare malignant tumors or to develop studies that may provide insight into the more common tumors.

The RFA, "Biochemical Epidemiology," issued by NCI, seeks applications for collaborative studies between laboratory scientists and epidemiologists in the application of a variety of sensitive and specific laboratory methods likely to facilitate epidemiologic investigations by providing better measures of exposure to initiators, promoters, anticarcinogens, and inhibitors of carcinogenesis. The usual epidemiologic techniques have been limited in their ability to reach firm conclusions by the difficulties in defining past carcinogen exposure levels and susceptibility states, in measuring low levels of risk, in evaluating directly host environmental interactions, and in identifying dietary determinants of cancer.

Modifying factors related to diet and nutrition have been implicated in several epithelial cancers including those of the gastrointestinal tract and reproductive organs. These types of cancers (among others) therefore might be especially suited for collaborative studies involving epidemiologists and experimentalists, including biochemists, analytical chemists, immunologists, and nutritionists. Appropriate interaction between epidemiologic and laboratory expertise should be evident in all phases of the proposed research from planning through implementation, analysis, and reporting.

Nutrition Conferences Sponsored by the NIH

Each year the NIH sponsors a number of conferences on a variety of nutrition topics that reflect the current interest of the Institutes in areas of program development for nutrition research and training. Such conferences also help to expedite transfer of nutrition technology to scientists and educators so as to assure the appropriate application of research in practice. Table VI lists the 13 conferences held in FY 1982.

TABLE VI

NIH SPONSORED NUTRITION CONFERENCES, FY 1982

<u>INSTITUTE</u>	<u>DATE</u>	<u>TITLE</u>
NIADDK	10/9-10/81	"Workshop on Guidelines for Research Methodologies for Use in Studies on Mineral Content of Human Tissues"
NHLBI, NIADDK, FIC	11/11-13/81	"Conference on Vitamin E: Biochemical, Hematological and Clinical Aspects"
NEI	11/16-17/81	"Nutrition, Pharmacology and Vision"
NIAID, NICHD	1/13-15/82	"NIH Consensus Development Conference on Defined Diets and Childhood Hyperactivity"
NCC	1/25-26/82	"Workshop on Body Weight, Health and Longevity"
NIADDK	2/14-19/82	"Fifth Workshop on Vitamin D"
NIADDK	4/29-30/82	"Nutritional Therapy in Chronic Renal Failure Conference"
NIA	5/8/82	"Assessment of the Evidence Relating Selected Vitamins and Minerals to Health and Disease in the Elderly Population in the United States"
DRG*	6/11/82	"Workshop on Nutrition and Endocrine Disorders"
NHLBI, NIADDK, FIC	6/21-25/82	"1982 Gordon Research Conference: Lipid Metabolism"
NIADDK, NCI, FIC	8/9-12/82	"1982 Gordon Research Conference: Food and Nutrition"
NICHD	8/30-9/2/82	"Workshop on Breast Milk Banking: Current Status and Future Needs"
NIADDK, FIC	9/1-4/82	"Third Congress on Nutrition and Metabolism in Renal Disease"

* Division of Research Grants

THE INTRAMURAL RESEARCH PROGRAM

The total cost of the NIH intramural program in biomedical and behavioral nutrition research was \$7,812,000 for FY 1982 (see table I). Institutes supporting intramural research in nutrition include NCI, NHLBI, NIDR, NIADDK, NIAID, NICHD, NEI, NIEHS, and NIA. Most of this research takes place on the NIH campus in Bethesda; however, the NIEHS staff conducts research in Research Triangle Park, North Carolina, and the NIA intramural program is located at the Gerontology Research Center in Baltimore, Maryland.

A major component of the intramural nutrition research program includes two interagency reimbursement agreements, one of NIA and one of NCI with the National Center for Health Statistics (NCHS) for the epidemiological followup of those participants of the Health and Nutrition Examination Survey (NHANES I), conducted in 1971-74. This survey collected dietary, biochemical, clinical and anthropometric information on the nutritional status of a national sample of the U.S. population comprising 23,000 persons between the ages of 1 and 74 years. The dietary data collected included calorie intake; calories as a proportion of RDA calories; nutrient density; protein, carbohydrate and fat as a proportion of total calories; number of carbohydrate servings per day; proportion of carbohydrate servings from complex carbohydrate sources and proportion of carbohydrate sources from individual food groups. The major emphasis of the followup survey is to relate the previously assessed dietary intake and biochemical test findings, chronic disease risk factors, environmental and occupational exposure and the psychosocial characteristics of the population with morbidity and mortality occurring since the original survey.

The NIA study includes a cohort of 14,400 persons, who were between the ages of 25 and 74 years at the time of the original study, in order to obtain specific information on dietary practices, alcohol use, exercise, smoking and changes in behavior over the past 10 years. Weight and blood pressure measurements are being made and related to previous measurements in order to assess changes in risk factors over time. The relationship between various nutritional factors and subsequent health status of the elderly is of particular interest in the hopes of improving the quality of life for all elderly persons.

The NCI is utilizing the NHANES I data to examine regional differences in vitamin A and vitamin C intake, and fruit and vegetable intake in relation to the North-South gradient in colon, rectal and breast cancer mortality. The intake of vitamin A, retinol, carotene and vitamin C (based on 24-hour recalls), the intake of vitamins A and C (based on food frequencies); the frequency of fruit and vegetable consumption; and serum vitamin A levels are being compared. Using the 24-hour dietary recall data, individual foods are being ranked by their contribution to total vitamin A intake for various age-sex-race region subpopulations. This information is being used in developing dietary interviews that will assess vitamin A intake and its relationship to cancer risk.

Also, the NCI is examining the possible effects of various factors including diet, age, sex, race, poverty status, pregnancy-lactation status,

region of inhabitancy, and individual variation on serum vitamin A levels from a national sample of 14,000 adults from NHANES I. The serum vitamin A levels are of interest since several prospective studies have shown that mean serum vitamin A levels are lower among those persons who develop cancer. A specific hypothesis being tested is whether serum vitamin A levels are significantly affected by vitamin A intake within a well-fed population such as the U.S.

Another component of NCI's research evaluates the NHANES I dietary and anthropometric data from 100 women between the ages of 12 and 18 years as predictors of age at menarche and in relation to the development of breast cancer. Studies have shown an inverse correlation between the age at menarche and the risk of breast cancer.

Other studies under way by NCI examine the relationship between nutrition and cancer etiology through basic research at the molecular level, particularly of skin cancer chemoprevention with vitamin A, and investigate differences of energy expenditure in tumor-bearing animals and the initiation of different cancers with various dietary components, such as saccharin. Dietary habits and nutrient consumption by selected cohort populations are being analyzed in relation to the incidence of different cancers, with investigations under way on general nutritional status, anthropometric and biochemical indices, as well as cooking practices. Another research priority is the assessment of the efficacy of total parenteral nutrition (TPN) for the support of the cancer patient.

Skin cancer chemoprevention through the use of vitamin A involves a great deal of research on the morphological effects, biochemical mechanisms, metabolic pathways, and dose toxicity of synthetic vitamin A (13-cis-retinoic acid) and its analogs in cell cultures and laboratory animals. Such research has provided important information on the cellular and molecular basis of skin carcinogenesis as well as the therapeutic value and antipromoting properties of vitamin A, before and after the onset of malignancy.

Other basic studies are investigating differences in energy exchange and expenditure in tumor bearing and normal animals through whole body calorimetry techniques. This research may help to elucidate the physiological basis of cachexia in the cancer patient.

An 18-month study is under way to investigate whether saccharin initiates or promotes human bladder cancer. Two additional investigations address the effects of specific fatty acids and lipotropes in modifying the uptake and resistance to carcinogens in mammary and liver cells. The impact of manipulation of hormones and dietary lipid intake on mammary tumor incidence is also being evaluated.

Several case control and cross cultural surveys are under way to study the incidence of colon, breast, esophagus, lung, pancreas, stomach, and other cancers in relation to dietary patterns of specific populations, biochemical and anthropometric indices, and general nutritional status. Case control studies have been initiated in high risk areas with unusually high mortality rates from cancer as well as among migrants such as the

Japanese Americans, whose changing cancer rates appear related to new lifestyles.

In order to assess the efficacy of TPN as a means of nutritional support for the cancer bearing host, prospective randomized studies of TPN as an adjunct to aggressive chemotherapy and radiation treatment are under way. Cancer patients receiving TPN are examined for deficiencies in vitamins, trace metals (zinc, copper, and chromium), and essential fatty acids, as well as for changes in gluconeogenesis, protein synthesis, glucose disposal, body composition for potassium, alanine kinetics, mineral balance, and requirements for all known nutrients.

The NHLBI has several intramural investigations that attempt to clarify the structure, biosynthesis, transport, and metabolism of lipoproteins since their moieties, i.e., cholesterol esters, triglycerides and apoproteins, have significance to the development of atherosclerosis. Research also continues on central neuronal systems and blood pressure regulation, since it is known that certain noradrenergic systems in the brain have a role in reducing blood pressure. For example, tyrosine has been shown to reduce significantly blood pressure in hypertensive rats. Other studies of stroke investigate the effect of dietary protein on the rate of protein synthesis in cerebral microvessels. Some data have shown that a low protein diet precipitates strokes in these animals. Genetic and environmental factors such as diet continue to be examined for their role in the development of hypertension.

Other research includes a randomized clinical trial of patients with chronic iron overload to assess the benefits or possible toxicity of ascorbic acid supplementation in the promotion of iron mobilization by disferrioxamine, a chelating agent for iron; a study of hematopoiesis in bone marrow failure; sterol metabolism in patients with beta-sisterolemia; the regulation of liver coenzyme A reductase; and the metabolism of lipids in human fibroblasts and muscle cells grown in culture.

Studies under way as part of NIDR's intramural program examine the effects of noncariogenic sweeteners on growth, acid production, and glucose synthesis by *Streptococcus mutans* in the mouth; and the effect of malnutrition on the composition of saliva and caries incidence. Because plaque pH is known to affect caries development, a device is being tested that would measure the pH of intraoral plaque when challenged with different foods.

The NIADDK conducts nutritional studies directed toward (1) determining the nutritional, biochemical, and metabolic roles of a variety of nutrients considered to be essential in the diet and (2) measuring the effects of different levels of nutrient intake on tissue levels of various metabolites in laboratory animals. These studies relate to dietary measurements, nutrient bioavailability, nutrient interactions, nutrient status, and metabolic function.

Intramural clinical research is also conducted on nutritional factors that relate to etiology, morbidity, and mortality of metabolic and other diseases. Of special significance are studies on bone metabolism and

osteoporosis; the role of vitamin D in various disease states; pathogenesis of human cystinosis; malabsorption, fatty acids, and membrane function in cystic fibrosis; diabetes mellitus and other chronic diseases of the Gila River Indians; the role of dietary carbohydrate and fat in modifying the action of insulin; the effect of weight reduction on glucose tolerance and glucoregulatory hormones; the pathophysiology of the adipocyte in human obesity; (Na^+ and K^+) ATPase activity in obese subjects; pharyngeal lipase activity and the digestion of dietary fats; the synthesis of prostaglandins in normal and transformed liver cells; the role of free inositol in brain, liver, and reproductive organs; very low density lipoproteins in Pima Indians; and the transfer of lipids, hormones, and enzymes in tissues, cell, and membranes.

Investigations on the mechanisms of food allergy supported by NIAID focus on the mechanisms of basophile and mast cell histamine and leukotriene release in the bowel, and ways in which food substances trigger that release. Histamine and leukotrienes are the pharmacological substances in the body which produce the tissue reactions recognized clinically as being allergic. Thus they may be responsible in part for the gastrointestinal upset, rashes, and other signs and symptoms of food allergies.

Studies carried out as part of the NICHD intramural nutrition program range from research on molecular genetics, inborn errors of metabolism, and endocrinological and reproductive research, to epidemiological research on breast feeding versus bottle feeding. Studies on genetic expression with nutritional deficiencies have shown that with a nutrient imbalance guanosine 3,5' bipyrophosphate (ppGpp) is involved in the expression of approximately one half of the *E. coli* genes, but has no regulatory effects during normal growth. Lethal consequences of the *rel S* mutation which abolished ppGpp accumulation during energy source starvation have been observed. The *rel A* and *rel S* double mutant is markedly defective in its ability to curtail cellular functions when adapting from luxuriant growth to nutritional impoverishment.

Research continues on various inborn errors of metabolism, including cystinosis, glutathione synthase deficiency, glutathionuria, gamma glutamyl-cysteine synthase deficiency, homocystinuria, glucose-6-phosphate dehydrogenase deficiency, phenylketonuria, galactosemia, and adrenal leukodystrophy. Investigators are interested in the development of nutritional therapy and new diagnostic measures. Discovery of the etiology of cystinosis and the identification of the first trans-membrane lysosomal transport system for amino acids has been made. Circadian patterns of hormones in children with Prader Willi syndrome and in normal obese children are being determined in order to detect any change in the pattern when the child achieves normal weight.

Children being treated for glycogen storage disease have shown significant improvements in maintaining normal blood glucose levels with the administration of corn starch every 6 hours. These studies also investigate the possible therapeutic effects of glucose, polycose, rice starch, potato starch, cooked corn, cooked potato and cooked rice containing equivalent amounts of complex carbohydrates in maintaining normal blood glucose levels in these patients.

A clinical trial is examining the safety and efficacy of cysteamine for the treatment of children with nephropathic cystinosis, a metabolic disease that leads to end stage renal disease before 10 years of age. Cysteamine's effectiveness will be evaluated by determining the creatinine clearance values of the treated children. The use of magnesium in infants with apnea and bradycardia is being investigated, since animals deficient in magnesium often develop these symptoms. Magnesium deficiency in animals appears also to manifest itself with retention of magnesium by the kidney. Since rat dams fed 150 mg of magnesium ($MgCO_3$) appear to suffer high fetal wastage, investigators are looking into the effect of feeding dolomite [$CaMg (CO_3)_2$] versus $MgCO_3$ in these animals.

The evaluation of thyroid function with diminished thyroid reserve and the changes in thyroid hormones during hypocaloric feeding in humans can now be demonstrated with the use of the pulse wave arrival time (QKd). Data have shown that with prolonged hypocaloric feeding, the QKd is prolonged, and therefore, suggests hypothyroidism at the target organ level. Oral supplementation with T_3 rather than T_4 prevents these changes in QKd. Changes observed in peripheral thyroid hormone levels during hypocaloric feeding appear to be due to adaptive mechanisms that result in hypometabolism.

Results from the study on trends in breast and bottle feeding in Pima women of the Gila River reservation have shown that parity had a positive association with bottle feeding. The highest proportion of bottle feeders occurred among women with small families before 1963 and with large families after 1963. Prenatal and postnatal care had a limited influence on the determinants of breast and bottle feeding. The study shows that mother and infant-oriented reasons dominated in the selection of breast or bottle feeding the first infant; while work related reasons had a stronger influence on the decisionmaking process for feeding the last child.

Another study of 1,275 American mothers, 800 of whom are breast feeders and 475 are bottle feeders, includes examination of independent and joint effects of various factors on the frequency and duration of breast and bottle feeding. These factors include prenatal and postnatal medical services; the mother's perception of support from peers, family and medical environments; confidence, enthusiasm and attitude of the mother toward breast feeding; sociodemographic factors; physiological conditions; and the initial feeding pattern, as well as changes over time.

NEI investigators are examining associations between specific nutrients and normal ocular health and function, as well as various ocular diseases. A new intracellular binding protein for retinoids has been identified in the subretinal space; research continues to elucidate the protein's role in ocular vitamin A metabolism and document its appearance at progressive stages of embryonic and newborn development. Concentrations of vitamins A and E in the pigmented rat retina and retinal pigment epithelium affect the formation and accumulation of lipofuscin pigment. Scientists are studying changes in lipofuscin associated with aging.

Cataracts and gyrate atrophy (an inherited disease due to a deficiency in an enzyme that metabolizes the amino acid ornithine) are two other areas of research attention by NEI. The various etiologies of cataracts being examined include the distribution of inorganic elements, such as copper, zinc, selenium, and calcium, in cataracts associated with retinal degeneration; the role of exogenous or endogenous oxidative stress in the formation of cataracts; and changes in the composition and metabolism of lipids of the plasma membranes and lenses. Inhibitors to the formation of cataracts through the limitation of aldose reductase activity are also being explored. Studies of gyrate atrophy attempt to determine how dietary manipulations or pyridoxine administration modifies ornithine levels and, in fact, arrest or improve conditions associated with the disease.

The NIEHS intramural nutrition program includes studies that examine the functional regulation of lipid assimilation in the gastrointestinal tract, since lipid transport and metabolism are important for the biological movement of environmental xenobiotics. Such studies measure the kinetics of lipid uptake into the cells and subsequent metabolism in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) sensitive and resistant strains of mice; identify changes in serum lipid transport, release and metabolism; and examine the formation and composition of lipoproteins from intestinal cells, lymph, and serum.

Nutrition as it relates to the aging process is being studied by NIA's intramural scientists in both animal models and human subjects. One area of interest is the mechanism(s) by which undernutrition affects various physiological functions with aging. In one study of male Wistar rats subjected to dietary restriction by alternate days of feeding and fasting, the normal age-associated loss of striatal dopamine receptors in the brain was substantially retarded. For example, the dopamine receptor concentrations in the striata of 24-month-old rats that had been on the restricted diet since weaning were 50 percent greater than those of the control animals of the same age given free access to food. In addition, the mean survival time of the rats on the restricted diet was 40 percent greater than that of the control rats.

Other studies on the effect of intermittent feeding as well as low protein feeding in animals reveal that low cellular protein levels result. The cellular activity of enzymes, however, was not consistently low in the tissues of the restricted animals.

The effects of age-related changes on the metabolism of specific nutrients such as fat and on physiological functions such as the regulation of salivary gland function are also being investigated.

Studies of age-related alterations of beta-adrenergic mediated lipolysis in the rat indicate that the amount and type of fat in the diet affect the hormone sensitive lipolytic response. Dietary fat was shown to have a profound effect on the lipid composition of cell membranes which in turn control the activity of numerous cell membrane enzymes including the hormone sensitive adenylate cyclase system.

Dietary fat, however, does not affect every tissue in the same way within the same animal, e.g., a diet high in unsaturated fat has little or no effect on fat cell membranes but greatly affects liver cells, which exhibit an increased hormone responsiveness to both catecholamines (epinephrine) and the polypeptide hormones (glucagon). In addition, a high fat diet inhibits to a large degree lipolytic responsiveness. The control of lipolysis with age is a complex area of nutrition research and will require further research on the interrelationships of diet and aging.

Research on the regulation of salivary gland function with age, i.e., the mechanisms that cause decremental changes with age, has demonstrated that with respect to the parotid gland at least one major secretory protein is significantly less in the aged animals.

An important aspect of the NIA intramural program involves human studies under way as part of the Baltimore Longitudinal Study of Aging (BLSA), initiated in 1958 to observe the same subjects over a long period of time in order to quantify true age changes and elucidate the mechanisms underlying these changes. The study group includes 1,000 male and female subjects, ranging from 20 to 96 years of age, who return every 2 years for reevaluation and are enrolled in the study for life. Cohorts from this study population are being examined for changes in oral health status, salivary gland function, taste thresholds, plasma lipids, and nutrient intake.

For example, demographic, socioeconomic and dental characteristics are being determined in 254 BLSA participants, who will serve as a basic study population for future cross-sectional and longitudinal investigations of aging and oral health status and function. One study of salivary gland function in BLSA subjects has shown a linear decrease in sodium secretion into the stimulated parotid salivary gland function with age. Males showed a greater decrease than females.

Studies on quality-specific variation in taste thresholds with aging include the detection of taste thresholds for the four basic taste qualities in 81 adults between 23 and 88 years of age. Data indicate that sodium chloride thresholds have a small but significant increase with age; quinine sulfate thresholds have a similar increase but are less significantly related to age; sucrose and citric acid thresholds are not significantly related to age; and citric acid thresholds appear to be different in males and females. Thus, the detection thresholds for the four taste qualities undergo different changes with age.

An analysis of plasma cholesterol values in BLSA participants show that levels increase in early adult life and decrease in late life. All age cohorts showed a significant decline in plasma cholesterol levels between the 1950's and 1970's. The change in body weight, polyunsaturated/saturated fatty acid ratio in the diet, and dietary cholesterol explains only a small percentage of this secular effect.

In order to gain insight on the nutrient intake across the adult age span, 180 BLSA male participants recorded 7-day dietary diaries during three

time periods: 1961 to 1965, 1966 to 1970, and 1971 to 1975. At the time of the first dietary diary, their ages ranged from 35 to 74 years. The analysis of the effects of aging, cohort, and time on diet utilized three research designs concurrently--cross-sectional, longitudinal, and time series. The nutrients considered were calories, protein, carbohydrate, fat, saturated fatty acids, polyunsaturated fatty acids, and cholesterol. The data indicate that the intake of calories, fat, saturated fatty acids, and cholesterol decrease with age. And over the time period, cholesterol and carbohydrate intake decreased, while polyunsaturated fatty acid intake increased. Cohort effects were not observed for any of the nutrients.

DRS provides support services to the intramural research of NIH. The DRS laboratory animal nutrition research program is responsible for improving the nutritional status of animals used in research and thus improve the overall quality of animal models. A series of feeding trials are designed to evaluate new diets and to determine the nutrient requirements of various strains or stocks of animals within a species. Data obtained from these studies form the basis for formulating diets having optimal nutrient concentrations for specific species of animals. These data are used to develop standard reference diets that are used throughout NIH, and ultimately by the entire biomedical research community. Diets with either deficient or excess nutrient concentrations are evaluated to provide animal models with nutrition-related diseases for study by NIH investigators. Studies are also conducted to develop satisfactory diets for the various animal species being introduced to biomedical research as new models.

NUTRITION RESEARCH TRAINING

The NIH supports training in biomedical and behavioral nutrition research in both the extramural and the intramural programs. Table VII summarizes the expenditures and the number of persons who received training in FY 1982.

TABLE VII
NIH TRAINING IN NUTRITION, FY 1982

<u>Institute</u>	<u>M.D. Degree</u>	<u>Ph.D. Degree</u>	<u>Other Degree*</u>	<u>Pre-Doc</u>	<u>Total Number of Persons Trained</u>	<u>FY 1982 Obligations (Dollars in thousands)</u>
EXTRAMURAL:						
<u>Institute Training Grants</u>						
NCI	4	4	4	5	17	318
NHLBI	20	71	0	0	91	828
NIDR	1	3	2	1	7	94
NIADDK	12	11	0	43	66	763
NIAID	6	3	0	0	9	8
NIGMS	22	1	0	45	68	250
NICHHD	12	5	2	0	19	154
NIA	0	0	0	30	30	4
Subtotal	77	98	8	124	307	2,419
<u>Individual Fellowships</u>						
NIDR	0	1	2	0	3	86
NIADDK	4	18	1	0	23	198
NIAID	1	0	0	0	1	6
NICHHD	1	5	0	0	6	56
NEI	0	3	0	0	3	47
NIA	0	2	0	0	2	22
Subtotal	6	29	3	0	38	415
EXTRAMURAL SUBTOTAL	83	127	11	124	345	2,834
INTRAMURAL						
NHLBI	6				6	133
NIAID	2				2	24
NIADDK	3	6			9	105
NICHHD	5	2			7	186
INTRAMURAL SUBTOTAL	16	8			24	448
NIH TRAINING TOTAL	99	135	11	124	369	3,282

* Other Degree includes M.D./Ph.D, Ph.D./D.D.S., D.D.S, D.V.M., D.Sc., etc.

Table VIII shows that for NIH as a whole the number of trainees and the financial support of these trainees remained relatively constant from 1978 through 1982. The number of trainees in the nutrition program, however, doubled between 1978 and 1979, and has since remained relatively constant with just a slight increase in 1982. The apparent decrease in the financial support for nutrition trainees in 1982 is the result of 18 trainees being supported from 1981 funds carried over in FY 1982. No carryover support was reported for FY 1981.

In terms of the number and financial support for fellowships, there appears to be an almost monotonic decrease in the number awarded by NIH, while except for 1980, the number of fellowships in the nutrition program has remained constant. The apparent decrease in the 1982 financial support of nutrition fellows per capita is the result of 12 fellows being supported by funds carried over from FY 1981. No carryover support was reported for FY 1981.

TABLE VIII

COMPARISON OF TOTAL NIH AND NUTRITION PROGRAM SUPPORT OF EXTRAMURAL RESEARCH TRAINING AND FELLOWSHIPS, FY 1978 - FY 1982
(in thousands of dollars)

Year	Total NIH				NIH Nutrition Program			
	Training		Fellowships		Training		Fellowships	
	Number of Trainees	Dollars	Number of Fellows	Dollars	Number of Trainees	Dollars	Number of Fellows	Dollars
1978	9,260	117,581	1,863	26,345	130	1,956	39	463
1979	9,204	116,193	1,993	27,468	261	2,555	36	466
1980	8,878	141,719	1,786	34,669	284	3,201	51	628
1981	9,121	144,719	1,574	30,897	268	3,159	36	549
1982	8,867	123,407	1,539	27,067	307	2,419	38	415

The research training activities in the extramural and the intramural programs are described below.

Extramural Training

Within the extramural program, two basic mechanisms are used for nutrition training support: institutional awards and individual awards.

The institutional national research service awards, commonly called "training grants," are designed to enable institutions to make training awards to individuals selected by them for predoctoral and postdoctoral

research training. In FY 1982, this mechanism was used to train 307 persons in nutrition for a total expenditure of \$2,419,000 in comparison to 8,867 full-time equivalent research trainees supported through training grants by all of NIH for a total expenditure of \$123,407,000. Nutrition trainees supported by training grants constitute 3.5 percent of all the trainees supported by this mechanism by NIH. This support represents 2.0 percent of NIH expenditures for FY 1982 training grants.

The postdoctoral individual national research service awards, called "fellowships," are awarded to provide postdoctoral research training to individuals to broaden their scientific background and extend their potential for research. In FY 1982, the NIH supported 38 fellowships in nutrition for a total expenditure of \$415,000, out of a total of 1,539 fellowships with a total expenditure of \$27,067,000. The number of fellowships in nutrition was 2.3 percent of the total number for NIH and the expenditure was 1.5 percent of the total NIH expenditure. Therefore, in the extramural nutrition training program for FY 1982, including both training grants and fellowships, a total of 345 persons were supported at a total expenditure of \$2,834,000. Thus, 3.3 percent of all NIH trainees were receiving training in nutrition in FY 1982. This effort accounted for 1.9 percent of NIH training expenditures.*

Examples of areas in which the trainees carried out their work include the following:

Nutrition and health status

Behavior, nutrition, hormones and seasonal rhythms

Pregastric satiety in experimental hyperphagia

Circadian rhythms and control of food intake

Regulation of lipolysis in animal and human obesity

Alpha-andrenergic regulation of hamsters' brown adipocytes

Influences on preadipocytes in culture

Genetic variation in human hormone sensitive lipase

Bioenergetics of fasting and lactation

Role of thermogenesis in body weight regulation

Studies of the dietary effects on human adipose tissue

Ovarian hormones, food intake and lipid metabolism

Control of food intake: focus on nutrition and behavior

* Source: 1983 NIH Data Book, Table 31, NIH Publication No. 83-1261, June 1983.

Nutrition and nephrology

Protein, amino acid and urea metabolism in humans

Epidemiology of cancer

Carcinogenesis and drug development

Experimental oncology and nutrition

Research in burns and trauma

Nutrition metabolism with trauma

Nutrition, lipid metabolism, and atherosclerosis

Lipid, lipoproteins and atherosclerosis

Lipoprotein methodology, structure and function

Chemistry of lipoproteins and atherosclerotic lesions

Cardiovascular epidemiology, biostatistics and nutrition

Cardiovascular disease prevention

Cardiovascular pathology

Cardiovascular pathophysiology and biochemistry

Target organ insensitivity to $1,25-(\text{OH})_2\text{-D}_3$

Vitamin D metabolism during pregnancy and lactation

Cutaneous formation and administration of $1,25-(\text{OH})_2\text{-D}_3$

Identification of $1,25-(\text{OH})_2\text{-D}_3$ metabolites

Synthesis and metabolism of vitamin D analogs

Characterization of vitamin D-like substances

The chemistry of vitamin B₁₂

Intestinal absorption and metabolism of riboflavin

Biotin: the mechanism of carboxylation

Biochemistry and biology of perinatal adaptation

Nutrition and perinatal biology

Interferon production in infants malnourished in utero, severely malnourished in developing countries, and in hospitalized U.S. malnourished children

The effect of interferon on immune defects of malnutrition

Interferon production before and after nutritional rehabilitation

Cultural and environmental factors affecting child malnutrition: Sudest Island Region, New Guinea

Fatty acids as an energy source in pregnancy and in the neonate

The role of biological rhythms in reproductive behaviors, cellular growth, and differentiation related to the biology of the neonate

The effect of aging on glucose tolerance and the ability to adapt to exercise

Transport of amino acids including nonmetabolizable amino acids across the blood brain barrier during development and senescence of rats

Parenteral branched chain amino acids in stressed patients

Nutrition and oral health

Effect of high levels of fluoride on developing tooth enamel

Interrelationships between nutrition and dental caries

The effect of food size and consistency on primate feedings

The role of pigment epithelium in supplying phospholipids or their precursors, including fatty acids to retinal photoreceptor cells

The role of zinc and vitamin A deficiencies independently and together in the development of the structure and function of the fetal retina and the level of retinal vitamin A

The role of lipids in light-induced degeneration of the retina; alpha tocopherol (vitamin E) loss and/or autooxidation of PUFA that limits the turnover of rod outer segment disks

Intramural Training

Within the NIH intramural program, four Institutes, NHLBI, NIADDK, NIAID, and NICHD, supported training of 24 scientists at an obligation of \$448,000 in FY 1982.

The intramural trainees worked in the following areas:

Glycogen storage disease

Metabolism of starch and starch rich foods

Cystinosis

Somatomedin in growth

Nutritional and pharmacological stimulation of lung maturation

Role of magnesium in fetal and postnatal maturation

Mechanisms of food allergy

Clinical studies in cystic fibrosis

Nutrition induced alterations in metabolism

Biochemical studies of hepatic and intestinal function

The role of prostaglandin synthesis in cell differentiation and transformation

Tryptophan synthase: mechanism of pyridoxal phosphate enzymes

Transport of lipids, hormones, and enzymes in tissues and cell membranes

The effect of weight reduction on glucose tolerance and glucoregulatory hormones

Pathophysiology of the adipocyte in human obesity

HIGHLIGHTS OF SPECIAL INTEREST AREAS IN NUTRITION

The highlights of nutrition research supported by the NIH in FY 1982 are presented in terms of 12 scientific areas and 3 areas in nutrition education. These 15 special interest areas reflect the scientific and political interest that has surrounded nutrition research in the most recent past and are described in decreasing order of expenditure. Similarly, the Institutes and DRR that support research in each particular area are listed in decreasing order of expenditure with the descriptive information.

Nutrition and Prevention of Disease

Research on Vitamins

Behavioral Studies in Nutrition

Child and Infant Nutrition

Nutrition and Genetics

Epidemiological Research in Nutrition

Nutritional Status

Nutrition and Obesity

Nutrition Education Research

Total Parenteral and Enteral Nutrition

Maternal Nutrition

Nutrition Education for the Public

Nutrition and Aging

Nutrition Education for Professionals

International Research in Nutrition

Table IX presents the number of grants and contracts in each area; the expenditure of the nutrition component of grants and contracts in that area; and the percentage of the total FY 1982 nutrition obligation of \$144,323,000. Grants and contracts pertaining to each area were designated by the program staff of the Institutes and DRR and may appear in more than one special interest area. For example, a study on the dietary treatment of phenylketonuric infants would appear in the following areas: child and infant nutrition, nutrition and genetics, and nutrition and prevention of disease. Therefore, the sum of each column in this table will exceed the corresponding quantities for the nutrition program as a whole.

TABLE IX
SPECIAL INTEREST AREAS IN NUTRITION--SUMMARY TABLE

<u>Special Interest Area In Nutrition</u>	<u>Number* of Grants and Contracts</u>	<u>Expenditure* (Dollars in thousands)</u>	<u>Percent** of Total</u>
<u>I. Research</u>			
Prevention of Disease	1015	\$ 87,601,000	61
Research on Vitamins	484	30,373,000	21
Behavioral Studies	252	29,979,000	21
Child and Infant	261	24,197,000	17
Genetics	181	18,946,000	13
Epidemiological Research	150	18,912,000	13
Nutritional Status	176	17,827,000	12
Obesity	187	17,118,000	12
Education Research	33	10,152,000	7
Total Parenteral and Enteral	88	8,801,000	6
Maternal	89	7,553,000	5
Education for the Public	17	5,897,000	4
Aging	88	5,861,000	4
Education for Professionals	72	5,014,000	3
International Research	30	2,245,000	2

*A grant or contract may be assigned to several special interest areas.

**The total expenditure of the nutrition program in FY 1982 was \$144,323,000.

Nutrition and Prevention of Disease

Research on the role of nutrition in disease prevention is supported by all NIH Institutes except NIGMS, i.e., NHLBI, NCI, NIADDK, NICHD, DRR, NIAID, NIEHS, NIA, NIDR, NEI, and NINCDS. In FY 1982, support in this area totaled \$87,601,000 or 61 percent of the total expenditures for nutrition research.

The definitions for prevention used by the NCC for data retrieval are as follows:

Primary prevention. Actions to promote health or undertaken prior to the development of disease; i.e., studies on nutrients to define nutritional requirements for health maintenance.

Secondary prevention. Detection of disease in its early (asymptomatic) stages and intervention to arrest its expression; i.e., the use of low phenylalanine diets in children with phenylketonuria (PKU) in order to prevent mental retardation.

Tertiary prevention. Intervention after the development of a clinically manifest disease in order to reverse or arrest its progression; i.e., studies on sodium excretion for the treatment of hypertension and on low sodium diets for the treatment of the "salt sensitive" hypertensive.

Prevention of disease begins early in life and involves many factors including the metabolic, cultural and behavioral aspects of nutrition and their effects on the nutritional status of infants and children. Research continues to attempt to define nutritional requirements of the fetus and neonate in order to prevent intrauterine growth retardation and to assure optimal fetal development, and the birth and subsequent growth of healthy babies. Optimal nutritional therapy is very important for the physical, mental, and functional development, and overall health and survival of premature infants in the face of biochemical immaturity; for infants and children with inborn errors of metabolism; and those infants with certain diseases or conditions such as lactose intolerance, celiac disease, necrotizing enterocolitis, food hypersensitivity, and other diarrheal and malabsorptive conditions. This research includes studies on human milk and human milk banking in order to identify and preserve specific components of human milk and colostrum for potential use in the nutritional therapy of high-risk infants.

Studies are under way on the role of breast-feeding as a means to reduce the incidence of acute diarrhea in infants due to E. coli and Clostridium difficile. The incidence and etiology of acute gastroenteritis due to these infective agents is being assessed in breast-feeding babies and in a matched control group not breast-feeding; i.e., infections are being analyzed with regard to specific antibody titers in human milk and serum, and with regard to the presence of rotavirus, E. coli, bacterial toxins, and C. difficile in the stools of mothers and their infants who develop diarrhea.

Malnutrition and intractable diarrhea or some other infective process that exacerbates the malnourished condition is a vicious cycle. Research on ways to rehabilitate the nutritional status of children suffering from diarrhea and the associated problems of nutrient absorption include the evaluation of the role of natural defense mechanisms of severely malnourished children. It appears that administration of fresh frozen plasma in three sequential transfusions helps to restore natural host defense mechanisms to a functional state, thereby allowing the child to fight the infection prior to any beneficial effects supplied by the nutritional therapy.

Recent studies on the cellular immune system of the normal human newborn infant have identified significant and selective maturational deficiencies. They include defects in specific cytotoxic and natural killer activities of the infant's blood. The specific regulatory mechanisms and cellular interactions need to be defined. Research in this area has specific implications for optimal infant feeding practices since infant formulas lack the immunological factors and other antimicrobial components present in breast milk and important to the prevention of neonatal infections.

Infant botulism represents the prototype of a new class of infectious diseases of infancy which involve the colonization of toxigenic spore forming bacteria in the infant gut and subsequent production of botulin toxin. This toxin produces a spectrum of diseases of varying clinical severity that can be manifest in its extreme form as crib death, also known as sudden infant death syndrome. Human milk has been shown to offer protection to the infant against toxigenic illnesses.

Nutritional therapy of infants and children with inborn errors of metabolism is designed to prevent or ameliorate the full expression of these genetic disorders. The therapy aims to minimize the patient's exposure to harmful nutrient substrates and to provide essential nutrients in required concentrations. Research on phenylketonuria (PKU), for example, has revealed that discontinuation of a low phenylalanine diet in children with PKU at age 6 was associated with higher blood phenylalanine levels (26.7 mg/dl versus 12.5 mg/dl for diet continuers) and significant differences in mean full I.Q. scores (98 versus 103 for diet continuers). Blood phenylalanine levels >20 mg/dl were associated with declining I.Q. scores. Children who remained on the low phenylalanine diet at 8 years of age showed a small but significant improvement in reading and spelling achievement tests from those children who discontinued the diet. However, improvements were not significant with the diet continued until ages 9 and 10.

Studies of maternal phenylketonuria investigate the placental transfer of phenylalanine and tyrosine in pregnant rhesus monkeys. Results suggest that 10 mg/dl of blood phenylalanine levels in the pregnant mother with PKU interferes with normal fetal central nervous system (CNS) maturation. Long-term studies to disclose what level of maternal blood phenylalanine will not damage the fetal CNS involve feeding pregnant monkeys a wide range of concentrations of L-phenylalanine in order to attain maternal mean blood phenylalanine levels of 5, 10, and 15 mg/dl throughout

pregnancy. At 6 months of age, the infants are exposed to a wide variety of training, memory and discrimination paradigms in order to assess any impairment in CNS development in terms of the maternal levels of blood phenylalanine. Additional studies on nutrition's role in the expression of various inborn errors of metabolism are described in the special interest area on "Nutrition and Genetics."

In an attempt to prevent adult obesity, studies are under way to control body weight in high risk preadolescent obese children. Investigators have demonstrated similar average weight changes after 2 years in parents and children assigned to behavioral weight control programs that are targeted to parents and children, children alone, and nonspecific weight loss targets. In terms of the treatment effects on the "maintenance" of normal weight, 100 percent of the children having parents participating maintained normal weight, while only 50 percent of the children treated alone, and 33 percent of the nonspecific control group maintained their weight. In addition, 83 percent of the children who lost weight maintained this new weight after 3 years if their parent participated in the program, while only 30 percent of those who participated alone maintained their weight. Research in this area also investigates the metabolic concomitants of obesity such as insulin resistance and glucose intolerance.

Studies of adolescents also investigate the nutrient requirements during puberty and adolescent pregnancy, as well as the problems of bulimia and anorexia nervosa. Behavioral and cultural aspects of the environment are being investigated as to their effect on the development of deleterious eating habits such as pica, food faddism, anorexia and binge eating, and the subsequent effects on nutritional status. Thus, much of the research in nutrition and prevention is concerned with the development of healthy adolescents to attain their genetic growth potential without obesity or malnutrition.

In order to understand the kind of preventive measures appropriate to the nutritional needs of the elderly, a number of studies attempt to elucidate the nutritional requirements with age, and the effect of body weight on health status in terms of longevity and disease states. Two studies examine the effect of nutritional status on immune function, i.e., the effect of protein malnutrition as well as tissue levels of a large number of nutrients on immune status.

In addition, studies of the elderly examine changes in taste and olfactory quality with age, the behavioral effects of undernutrition and aging, the effects of various living arrangements on dietary habits, stress and subsequent nutritional status, and the role of vitamin D in the prevention and treatment of osteoporosis in postmenopausal women.

Studies of osteoporosis in postmenopausal women have shown that daily doses of as little as 0.5 micrograms of 1,25 dihydroxycholecalciferol to postmenopausal women with osteoporosis increased calcium balance, and also increased trabecular bone volume and decreased bone fracture rate. These investigators have shown that after age 50, especially in postmenopausal women, plasma levels of 1,25 dihydroxycholecalciferol decrease

significantly. Estradiol treatment of these women caused a 30 to 40 percent increase in circulating levels of 1,25 dihydroxycholecalciferol and a corresponding increase in calcium absorption. Other studies have shown alpha hydroxycholecalciferol effective for the treatment of post-menopausal osteoporosis since the alpha form is readily converted by the liver into the active 1-25 dihydroxy active form.

Current knowledge about the endocrine function of vitamin D₃ metabolites, their isolation and chemical characterization, has led to their widespread use to treat a variety of metabolic bone diseases such as renal osteodystrophy, hypoparathyroidism, pseudohypoparathyroidism, vitamin D resistant rickets as well as osteoporosis. In addition, measurements of the vitamin D metabolites are being used to diagnose a variety of diseases, e.g., low plasma levels of 25-hydroxycalciferol indicate intestinal malabsorption, biliary secretion failure or poor vitamin D nutritional status.

Research on another important vitamin, vitamin A, attempts to uncover its role in vision and the prevention of blindness, as well as its role in the immunocompetence of ocular tissue and its subsequent ability to respond to trauma. These studies attempt to develop animal models of xerophthalmia and keratomalacia in order to assess also the role of infection. The prevention of cataract formation is being examined through studies that modify the activity of certain enzymes such as aldose reductase, and the rate of accumulation of oxidation products such as levels of vitamins C, E, and A.

Other research on micronutrients and their role in disease prevention examines the modulating effect of trace elements such as zinc and iron on microbial virulence. Results from this research have shown that zinc deficiency not only damages cell mediated immunity in animals, but also impairs the animal's ability to control mycobacterial insult, e.g., tuberculosis infections. Protein deficiency augments this adverse effect. The animal's immune system depends more on current nutritional status, rather than a history of malnutrition indicated by reduced body weight.

New evidence on the mechanisms of microbial virulence has shown that the iron required for the growth and virulence of intracellular bacteria, such as Salmonella, is obtained from ferritin located within macrophages rather than from transferrin in blood. Also, lymphocyte uptake of the transferrin needed for their activation is inhibited by serum low density lipoproteins (LDL). Macrophages, however, can reverse the inhibitory effect of LDL by a direct effect on the LDL molecule itself.

Various nutrients, especially the amino acids, are known to affect central nervous system (CNS) development and function. A study of free lysine metabolism in the brain has shown that lysine is actively metabolized in the brain via the pipercolic acid pathway, and that some of the metabolites may have physiological functions as neurotransmitters and neuromodulators. They may therefore play an important role in certain neurological functions and conditions, i.e., sleep, sedation, schizophrenia, etc.

Other peptides present within the CNS (cholecystokinin, thyroid releasing hormone, and insulin) are involved in the regulation of feeding behavior

and, therefore, in the control of body weight. Cholecystokinin (CCK) peptides are present in the brain in high concentrations, especially in the cortex and hypothalamus. Research in sheep has shown that CCK is extremely potent in suppressing feeding behavior when injected into the cerebral ventricles, whereas injections of CCK antiserum into the cerebrospinal fluid (CSF) block satiety.

One hypothesis is that CCK is released into the brain during feeding, possibly into the ventricular system, transported via the CSF, and acts on CNS receptors involved in the elicitation of satiety. Investigators are attempting to determine the sites and rates of release of CCK into the CSF during hunger and satiety as well as sites of action of brain CCK in causing satiety. Interaction of the ventromedial hypothalamus with the noradrenergic system has been proposed as a possible site of action. Suppression of feeding by CCK has also been reported to be mediated through a parenteral abdominal site.

The neuroanatomical organization of the nervous system that controls food intake and body weight regulation is being elucidated and will help to develop possible therapeutic approaches to obesity. The relationship of spontaneous obesity to monoamine function is being investigated in studies of genetically obese mice where abnormalities in the catecholaminergic system have been detected. The contribution of central catecholamines to disturbances in autonomic functions related to feeding behaviors and body weight is being examined.

Additional studies on the central nervous system development in rats seek to determine whether undernutrition early in development causes abnormalities in the synthesis or structure of gangliosides and glycoproteins in synaptic plasma membranes (SPMs). Data have shown that the offspring of rats fed either a protein-calorie deficient diet or protein deficient diet during lactation had a marked deficit of SPMs, which was greater in the forebrain and hippocampus than in the cortex or cerebellum.

The role of cobalamin in nervous tissue and its interaction with other nutrients, especially folate, is being investigated in the fruit bat (*Rousettus aegypticus*) since these animals, when made deficient, develop neuropathy without hematological cobalamin complications.

Fiber is another dietary component under investigation for its possible effect on disease prevention. Studies attempt to determine the chemical characteristics of various fiber components, to develop the appropriate methods for measuring dietary fiber, and to evaluate the effect of different forms and sources of dietary fiber components on the digestion, absorption, and bioavailability of nutrients. Some methods suggested as suitable for hydrolyzing food and fecal neutral detergent fiber (NDF) are the Saeman hydrolysis procedure as modified by Selvendren, and short periods of amylase treatment.

The various forms of fiber being studied include cellulose, xylan, pectin, corn bran, and wheat bran. Cellulose or wheat bran have been shown to decrease digestive enzyme activity in the small intestine either by dilution of the contents, or by interfering with enzyme activity. Pancreatic

enzyme activity, however, increased with the ingestion of wheat bran. In terms of fiber's effect on the bioavailability of minerals, differences may be due to variations in the fiber composition of natural fiber sources. Studies compare the effects of cellulose, xylan, pectin, and corn bran on the bioavailability of calcium, magnesium, phosphorous, iron, copper, zinc and selenium.

One study of pectin reported a decrease in B₁₂ bioavailability which, however, did not result from an interference with absorption due to calcium binding. Xylan, a bacterially digestible dietary fiber, was shown to increase liver and fecal folate levels beyond those levels provided by the diet, thereby suggesting that bacterial synthesis of folic acid was enhanced in the intestine. The effects of fiber on metabolism, therefore, may relate to the alterations in the rate of digestion and absorption of these various nutrients from the small intestine.

The possible beneficial effects of fiber in the diet are being studied in cancer patients, and in diabetic patients including pregnant women in order to test the hypothesis that a high fiber diet may reduce the diabetic's need for insulin.

Research on nutrition and prevention deals with nutrition's role in the prevention of specific diseases such as cancer, coronary heart disease, atherosclerosis, hypertension, diabetes, osteoporosis, diverticulosis, dental caries, etc. A number of studies investigate the effect of specific nutrients and other food components on the initiation, promotion and inhibition of carcinogenesis in the pancreas, liver, breast, esophagus, oral cavity, and lung.

Initiation of pancreatic carcinogenesis by coffee, and colon carcinogenesis by cycasin, methylazoxymethanol, 1-2 dimethylhydrazine, and azoxymethane is being investigated. Examinations are under way on changes in intestinal microflora and tissue enzymes, including protein kinases and phosphoproteins. Diets deficient in methyl groups are also being studied in terms of the initiation of liver and pancreas carcinogenesis in the azaserine rat model.

Other investigators have shown that ethanol acts as a carcinogen in nitrosamine carcinogenesis by increasing the metabolic activation of the target organ. Studies are under way to examine the increased risk with ethanol intake for cancer of the oral cavity, esophagus, and larynx, and the expression of carcinogenicity with liver damage.

Studies on the role of fat, especially levels of unsaturated fatty acids in the diet, attempt to provide more insight into the mechanisms of induction and promotion of cancer, as well as the simultaneous physiological effects observed with cyclopropanoid fatty acids. The murine model is being used in breast cancer studies in order to analyze the effect(s) of a polyunsaturated fatty acid (PUFA) diet on dimethylbenzanthracene (DMBA)-tumorigenesis and/or preneoplasia in BALB/c mice. The effect of PUFA promotion on the number and phenotypic properties of altered cells is being determined during latent tumor periods and in the presence of cancer promotion regimens. Saturated fat in the form of beef tallow,

unsaturated fat in the form of corn oil, and a blend of fat found in the typical American diet are being tested for their effect in stimulating mammary neoplasia after DMBA administration. The sources of fat found in the American diet can be grossly categorized into meat and poultry (40 percent), butter and dairy products (14 percent), margarine and shortenings (22 percent), salad and cooking oil (17 percent), legumes and grain products (7 percent). The blend of fat used in this study consists of beef tallow (27 percent), lard (13 percent), butter fat (14 percent), partially hydrogenated fat (22 percent), soybean oil (10 percent), peanut oil (7 percent), and corn oil (7 percent). The inhibitors of mammary carcinogenesis, propylgallate and butylated hydroxytoluene (BHT), are also being tested in terms of their effect with different types and amounts of fat. Structural or functional changes in the mammary gland will be assessed.

The inhibition of carcinogenesis is being studied using the P-450 mono-oxygenase enzyme system in the liver. Tests of chemical inhibitors and flavenoids attempt to alter the balance between activation and detoxification pathways in order that activation may be diminished. The chemopreventive agents such as flavenoids, disulfiram, ascorbic acid, selenium, glutathione, phenolic antioxidants and protease inhibitors are being examined in terms of their interactions with a variety of chemical carcinogens and the resultant chromosomal instability. Quantitative assays of the chemopreventive agents are being used to determine which agents inhibit tumor induction at specific stages, as well as the mechanism of action.

In addition, diet related cancer inhibitors such as butylated hydroxy-anisole (BHA), cinnamic acids, coumarins, aromatic isothiocyanates, indoles and their derivatives are also being tested for their inhibitory activity. The levels of electrophiles available to react with DNA alkylation by N-nitroso-dimethylamine (DMN) and N-nitroso-diethylamine (DEN) in mouse lung and rat liver of BHA treated and control animals are being studied. This research attempts to unveil the mechanism by which these compounds may inhibit carcinogenesis, in an effort to develop a practical approach to the chemoprevention of cancer by low level exposures to environmental nitrosamines.

Butylated hydroxytoluene (BHT), an antioxidant added to foods at very high levels, is being studied along with glucocorticoids known to inhibit the proliferation of Type 2 cells from adenomas, accelerate the differentiation of these cells, and inhibit the toxic effects of BHT on mouse lung. In order to understand the mechanism by which BHT promotes tumors in the lung, this study will attempt to determine BHT's effect on the glucocorticoid receptors. Other studies on antioxidant action relevant to cellular processes found in carcinogenesis and tumor promotion are investigating benzopyrene metabolism and prostaglandin synthesis. Changes in the pattern of prostaglandin synthesis by the action of the antioxidant on the free radical will be determined. In addition, the interaction between the antioxidants and the electrophilic intermediates from activated esters of oncogenes *in vivo* are being ascertained in an effort to protect against mutagenesis *in cell culture*.

Folic acid is being studied for its possible role in the promotion of cancer cells back to normal and in the prevention of the progression of early cancer cells. In one study of 47 women on combination type oral contraceptives and having abnormal pap smears, a daily regimen of folic acid significantly improved cytology scores. Deficiencies of copper, magnesium, and zinc are also being investigated in terms of their effect on cytotoxic T lymphocyte generation. Such mineral deficiencies may have an important effect on cancer promotion, and therefore amelioration of these conditions may improve cancer prevention.

A number of studies investigate the risk factors of cardiovascular disease in order to develop appropriate intervention strategies, either on a community or individual basis. Community demonstration studies have been successful in establishing coronary heart disease prevention programs in community organizational settings, churches, and schools. Various kinds of material have been developed on blood pressure control, weight control, and smoking cessation. Research continues to investigate the long-term effect of these community programs on cardiovascular disease morbidity and mortality. Attempts to modify cardiovascular disease risks are also being made through behavior programs designed for families.

Specific dietary components, such as alcohol and lipids, are being studied in terms of their effect on coronary heart disease. Results from the research on alcohol consumption indicate that the relationship of drinking behaviors to health outcomes is complex and that it is premature to recommend even moderate drinking as protection against coronary heart disease.

Studies of Greenland Eskimos revealed lower plasma lipid levels and a lower incidence of atherosclerotic diseases probably related to their diet of fish and seal. As a result of these findings, the antiatherogenic properties of the omega-3 fatty acids, found in fish and seal, are being investigated in patients with hyperlipidemia. One study includes feeding a salmon oil diet containing large amounts of these fatty acids, a vegetable oil diet high in linoleic acid, and a control diet high in saturated fat. The salmon oil diet was found to reduce plasma cholesterol and triglyceride levels more effectively than the vegetable oil, and the omega-3 fatty acid constituted up to 30 percent of the total fatty acids in each plasma lipoprotein class.

Another study in monkeys is also investigating the effects of a fish oil diet on the natural history of coronary and cerebral artery arteriosclerosis. Evidence from the study suggests that the atherosclerosis sparing effect of fish oil is due to the eicosapentanoic fatty acid's preferential incorporation into the platelet membrane phospholipid. This incorporation changes platelet function in ways favorable to diminishing atherosclerosis. These findings suggest that fish oils contain fatty acids that may be metabolically unique and potentially useful in the control of both hypercholesterolemia and hypertriglyceridemia, and therefore, in the prevention of atherosclerosis.

Additional work on atherosclerosis has revealed that cholesterol ester hydrolase (CEH) activity is lower in the mononuclear cells of patients with symptomatic atherosclerosis, as well as in those with hyperlipidemia

and diabetes. The hypothesis being tested is that lower CEH activity in the intimal smooth muscle cell causes impaired cholesterol ester hydrolytic activity and thus increases the risk of progressive atherosclerosis. It is hoped that blood monocytic CEH activity is predictive of intimal smooth muscle cell CEH activity, and therefore, those individuals at high risk may be identified prior to the occurrence of serious, atherogenic complications. Studies of CEH activity are under way in high risk patients such as those with diabetes mellitus, familial hypercholesterolemia, and a history of strokes or transient ischemic attacks.

Some investigators are testing changes in the progression or regression of atherosclerotic plaques in patients consuming the usual American diet and a cholesterol lowering diet. From studies of nonhuman primates, plaque progression and regression has been related to the rates of influx and efflux of cholesterol from the plasma. Therefore, these studies attempt to determine the cholesterol turnover rate of both free and ester cholesterol pools, the rate of cholesterol esterification, and the rate of cholesterol ester glycolysis in the diseased artery wall. Subsequently, the effect of the cholesterol lowering diet and/or drugs on these metabolic rates will also be determined.

Investigations continue to explore various methods to prevent and control hypertension, a disease that affects approximately 60 million Americans. Interim findings from one study imply that a high proportion of individuals with mild hypertension may control their blood pressure with little or no medication if weight control and sodium restriction is achieved. Biological as well as sociocultural variables related to hypertension were examined in another study of 8,000 Japanese men living in Hawaii. A multivariate analysis of this study's data indicates that obesity, age, hematocrit, heart rate, forced vital capacity, serum triglycerides and uric acid levels, cigarette smoking, and a family history of hypertension are independently associated with cross-sectional levels and longitudinal changes in hypertension.

Knowledge of specific risk factors for hypertension allows for the development of appropriate messages used in educational and behavioral modification prevention programs. Two demonstration and education research studies are exploring the possibility that dietary changes and/or relaxation training will reduce or eliminate the need for medication in hypertensives, and that paraprofessionals and nonclinic settings such as the workplace and community sites are appropriate for the non-pharmacological treatment of hypertension. A cost effective study of specific interventions to improve blood pressure control in defined populations is also under way and will provide important insight on the cost of preventive intervention strategies.

Research on the nutritional implications of kidney disease has shown that management of these patients requires restrictions of sodium, potassium, phosphate and fluids. Progressive loss of kidney function changes additional endocrine and metabolic functions. For example, with advanced renal failure, vitamin D₃ is not converted to 1,25 dihydroxycholecalciferol D₃ and therefore calcium homeostasis is affected, resulting in uremic bone disease. In addition, these patients experience insulin

resistance and therefore require higher levels of insulin to achieve control of glucose levels; and have altered carbohydrate, fat, and protein metabolism, and differences in vitamin requirements. A variety of projects are devoted to either the basic mechanistic understanding of these differences in metabolism or the practical issues of patient requirements.

Nutritional therapy for the treatment of patients with chronic renal failure has important implications for reducing the frequency and perhaps the need for dialysis. Low protein diets have been shown to maintain non-dialyzed chronically uremic patients relatively free of uremic symptoms. Two low protein diets, namely, one providing .55-.60 grams/kg/day of high quality protein and one providing 20 grams/day of varied quality protein as well as 20.7 grams/day of nine essential amino acids, have been successful in maintaining near normal serum protein levels and anthropometric measurements. They also appear useful for extended periods of time.

Patients with end-stage renal disease but with some residual renal function, also have been successfully maintained with low protein diets coupled with reduced frequency dialysis. For example, patients either on a diet of 0.96 ± 0.12 grams/kg/day of protein at 65 percent high biological value, or on a diet of 0.4 grams/kg/day of protein at 40 percent high biological value plus 10 grams/day of essential amino acids, maintained a positive nitrogen balance for 2 to 6 months, had lower concentrations of blood urea nitrogen, normal serum protein levels and normal nerve conduction velocities. More studies will be conducted in this area since successful rehabilitation of these patients with nutritional therapy coupled with reduced dialysis frequency would be a considerable cost savings.

Other research on chronic renal failure is under way in a rat model in order to observe the possible consequences of a high phosphate diet on the loss of kidney function. Rats on the higher phosphate diets were shown to have higher serum calcium levels, and more calcification and adverse histological changes in the kidney. This research lends support to the hypothesis that higher phosphate diets accelerate kidney function loss through calcification in the cortical tubular cells, basement membranes, and interstitium, occurring in the course of renal failure.

Tooth decay affects most children as early as primary teeth erupt. By 11 years of age, the average American child has three permanent teeth attacked by caries, while by 17 years of age, eleven permanent teeth have decayed, been filled, or are missing. Prevention efforts are aimed at making teeth less susceptible to caries by use of fluorides and by decreasing the frequency of sugary foods.

Research on nutrition's role in the prevention of dental caries, therefore, includes studies to develop noncariogenic sweeteners. In recent years, plant derived sweeteners used by native populations in other countries have shown promise for use in the U.S. Scientists have isolated, purified, characterized and subjected to a taste panel all the sweet principles from *Stevia rebaudiana*, a plant native to Paraguay. Extracts from this plant are used in Japan in commercially produced

foods such as chewing gum, soft drinks, sauces and pickles. Other alternate sweeteners used by native populations are under study from the following plants: Hydrangea thumbergia, native to Japan; Mormodica gros-veneri, native to Southern China; and Lippia dulcis, native to Mexico. A number of tests for potential health hazards of these sweeteners will be required before they are released in the market place.

In addition to sugar, other factors known to modulate the cariogenicity of foods include eating frequency, presence of cariostatic agents, food texture, food stickiness, induction of salivation, etc. To examine these factors, scientists have developed a highly reproducible rat model that provides by intubation essential nutrition as well as 17 daily snack foods at hourly intervals. The cariogenic potential index (CPI) of a food is the ratio of the caries scores resulting from the ingestion of the test food compared to powdered sucrose. The CPI of foods tends to increase with increasing sugar content, as in the case of breakfast cereals. However, some results indicate that the elements in food that give rise to an increased CPI are not fully understood. This rat model shows great promise in examining the complex relationship of those factors important to the cariogenicity of a particular food. Because the test food is the only food that comes into contact with the rat's oral cavity, this rat model can be used to measure the relationship of a food's CPI value and other parameters such as the salivary enzyme activities and the presence or absence of immune factors.

Research on Vitamins

Research on vitamins includes studies to determine their requirements in specific age groups, particularly in the fetus, neonate, and the elderly; the metabolic processes in normal as well as transformed cells; and their interrelationships in the intact organism. In FY 1982, NCI, NIADDK, DRR, NICHD, NEI, NHLBI, NINCDS, NIDR, and NIA supported \$30,373,000 or 21 percent of total nutrition expenditures on research in this area.

A number of studies are investigating the role of vitamin A in the differentiation of epithelial tissue and in fetal growth and development. Dietary requirements of vitamin A during pregnancy and lactation have not been thoroughly determined and few data exist on fetal and neonatal requirements. It is likely that vitamin A requirements vary with protein intake when this intake is inadequate. Studies are under way to evaluate the hepatic, renal and gastrointestinal controls of the mother's metabolism of vitamin A and related compounds; to characterize placental transport, especially of retinol when vitamin A intake is low or excessive; and to examine the effect of supplemental doses of vitamin A on placental transport, fetal metabolism and the trans-placental retinol transport system. Data indicate that placental transport of vitamin A decreases with excessive maternal intake or when maternal stores are high, and increases when stores are low. Examination of vitamin A metabolism in the maternal-fetal-neonatal unit must include examination of the effects of protein intake since vitamin A transport, storage and utilization all are influenced by protein intake. Vitamin A is also being examined for its effect on the development of teeth and bones since deprivation of the vitamin in rats leads to increased caries development.

In terms of the molecular mechanisms of vitamin A, intracellular binding proteins for retinol and retinoic acid have recently been characterized. Retinol and retinoic acid have been shown to influence genomic expression in vivo by activation as well as suppression of the genome; the binding protein for retinol (CRBP) delivers retinol to the nuclei of rat liver cells where it associates with the chromatin. The protein does not remain bound. The retinol-chromatin interaction presumably affects the genomic expression underlying cell differentiation.

Investigations on the teratogenic effects of excess vitamin A and zinc deficiency in rats have revealed a high incidence of fetal malformations from either treatment, but no interaction between them. Brain deformities resulted under both conditions; excess vitamin A resulted in a higher incidence of fetal eye and palate anomalies than the zinc deficiency, but had no effect on DNA synthesis. Zinc deficiency caused a higher incidence of lung and tail malformations and a low uptake of H^3 thymidine into embryonic DNA.

A major focus of vitamin A metabolism is on its role in the visual process and in the integrity of ocular epithelium. The enzymatic mechanisms by which 11-cis-retinaldehyde is formed from all-trans retinal and bound to protein in the formation of rhodopsin is under investigation in photoreceptor cells. Other studies are looking at the effect of vitamin A deficiency alone as well as with calcium and zinc deficiencies on dark adaptation; the role of specific ocular retinol binding proteins in the intracellular transport of retinoids between the retinal pigment epithelium and rod outer segments; the effect of aging on the efficiency of vitamin A utilization for rhodopsin formation; vitamin A's role in the corneal response to infection and trauma, particularly as this relates to corneal melting and keratomalacia, the prevalence of xerophthalmia and keratomalacia and associated risk factors for their development in India; and a new approach to the assessment of vitamin A status in children with and without various degrees of protein-calorie malnutrition.

Studies of the modulation, mediation, prevention and treatment of cancer with vitamin A and its retinoid analogs comprise a large portion of research in this area. A number of animal models are being used to investigate the effect of moderately high and marginally low vitamin A supplementation on the initiation and promotion of carcinomatous and benign mammary tumors in rats treated with dimethylbenzanthracene (DMBA) and methylnitrosourea (MNU); the effect of retinoids and selenium on the inhibition of bladder carcinogens; and the effects of retinoid and difluoromethylornithine on cancer incidence, latency, and tumor number.

In order to understand the molecular mechanisms of retinoids that alter intracellular events resulting in abnormalities in cell growth and carcinogenesis, the ability of retinoids to inhibit ornithine decarboxylase induction and increase RNA synthesis is being evaluated in isolated nuclei from proliferating and retinol arrested cells. The possibility that retinoids may act as corticosteroids and inhibit collagenase production at some level of mRNA transcription is being tested using phorbol myristate acetate treated synovial fibroblasts from rabbits. Other studies consider the antitumor activity of retinoids in terms of the

stimulatory effects on the immune system; retinoic acid is thought to promote lymphoid differentiation in the retinoid-mediated neutralization of tumor promotion by phorbol ester. The mechanism of 13-cis retinoic acid and the secretion of a single glycoprotein in mouse skin tumors is being evaluated to determine the relationship of the glycoprotein induction to mucous metaplasia and tumor regression. Results from such research will be useful in designing synthetic retinoids that enhance chemopreventive activity.

Studies of cancer patients have shown that those patients with low levels of vitamin A have more recurrence of disease. Patients with Stage I and Stage II melanoma are under study in order to determine if adjuvant therapy with vitamin A can prevent recurrence of their cancer.

The various aspects of vitamin D metabolism being studied include vitamin D requirements of term and premature infants, especially in terms of the clinical problems of neonatal hypocalcemia, infantile rickets and osteopenia. Studies suggest that late neonatal hypocalcemia, manifested by low total serum calcium, low parathyroid hormone and magnesium levels, and elevated phosphorous levels could be due to a defect in parathyroid hormone secretion perhaps related to a defect in magnesium metabolism. Vitamin D's role in the mechanism of this condition needs further investigation.

Since vitamin D is known to affect the rate of bone collagen maturation, one investigator has developed models of hypo and hypervitaminosis D in the suckling rat, and a new technology for determining the distribution and amounts of reducible and stable bone collagen cross links. The formation of covalent cross links in collagen contribute to the tensile strength of the collagen. In bone the intermolecular cross links predominate over the intramolecular cross links. Research has shown that with age, covalent cross links are reduced *in vivo* to the more stable cross links; results of this research as well as a clearer understanding of the role of the calcium, phosphorous and calciferol metabolites on bone mineralization are important to understanding the nature of the defects of mineralization in rickets and osteomalacia.

Two distinct mechanisms have been identified whereby intestinal calcium transport responds to the active form of vitamin D; one is by an initial response by existent villus cells and the second is a crypt cell response whereby calcium transport begins as the cells move into position on the villus membrane. Studies of osteopenia in chronic cholestasis have shown that serum 25-(OH) vitamin D₃ levels correlate with intestinal calcium absorption, although these parameters were not predictive of the histology of metabolic bone disease.

It appears from studies in rats that the majority of vitamin D₃ and 25-(OH) vitamin D₃ is transported from the jejunal sacs in the portal blood rather than the lymph, and that the absorption of 25-(OH) vitamin D₃ is greater than vitamin D. 1,25-(OH)₂ vitamin D₃ is transported also mainly in portal blood and is not dependent on chylomicron production. Although bile salts increase the amount of 1,25-(OH)₂ vitamin D₃ in the lymph, total absorption is only slightly increased. One investigator has shown

that the pituitary gland, vis a vis growth hormone, is necessary for maintaining elevated 1,25-(OH)₂ vitamin D₃ plasma levels during phosphate deprivation. In studies with chicks, the pure form of the 1,25-(OH)₂ vitamin D₃ receptor from intestinal mucosa has been isolated and four new vitamin D metabolites have been identified.

Patients undergoing hemodialysis appear to have a substantial reduction of photoactivation of vitamin D, despite the presence of normal concentrations of the substrate of 7-dehydrocholesterol in the epidermis. This finding represents an exciting new lead into the process of vitamin D activation in the epidermis. Establishing the appropriate dosage of the activated forms of vitamin D to treat more effectively children with diseases that lead to hypocalcemic disorders is an important research area.

High performance liquid chromatographic techniques have been used to assay vitamin D₂, vitamin D₃, 25-(OH) vitamin D₂, and 25-(OH) vitamin D₃ using very small samples in human milk. Preliminary results indicate that 25-(OH) vitamin D₂ and 25-(OH) vitamin D₃ occur in breast milk at concentrations of less than 0.5 mg/ml. Studies are investigating the use of enzymatic hydrolysis in order to release vitamins D₂ and D₃ from the breast milk lipids and the development of microassays for 1,25-(OH)₂ vitamin D and 24,25-(OH)₂ vitamin D. Additional research is under way to determine the role of vitamin D and its metabolite 1,25-(OH)₂ vitamin D₃ on lactation and its interaction with parathyroid hormone, calcitonin, and prolactin. Lactation represents a unique physiological condition for the study of the interaction of calcium-regulating hormones.

Vitamin E research deals with basic studies on its reduction potential, as well as the development of new assays and analogues of vitamin E. In studies on the use of vitamin E in the various hemolytic anemias, it appears to ameliorate the oxidative ravages of insufficient amounts of reduced glutathione in the anemias of glucose-6-phosphate dehydrogenase deficiency and glutathione synthase deficiency. Clinical investigations continue on the vitamin E requirements of premature infants by evaluating such factors as the presence of malaise, poor feeding, failure to thrive, infections, necrotizing enterocolitis, and bleeding problems in infants with low levels of vitamin E. The protective role of vitamin E in retrolental fibroplasia in premature infants is also being investigated.

Preliminary studies of the mechanism of action of vitamin E on platelet aggregation, release and adhesive properties suggest a direct influence of the vitamin on the fluidity of platelet membranes. It is hypothesized that vitamin E makes arachidonic acid in the membrane unavailable for oxidative conversions by cyclooxygenase and lipoxygenase. Vitamin E appears to be an effective *in vitro* inhibitor of platelet aggregation and release, and one of the few physiological antiaggregates. The *in vivo* effect of vitamin E supplementation alone and in conjunction with aspirin on platelet function will be evaluated in normal volunteers.

Investigators have shown that vitamin E in selenium deficient rats protects against lipid peroxidation in rats treated with 50 mg. of methyl ethyl ketone peroxide per kg body fat, as measured by pentane production.

Chronic ethanol consumption for 9 weeks did not influence lipid peroxidation in vitamin E and selenium deficient rats, even though the vitamin E deficient rats produced twice as much pentane as rats fed vitamin E. Another study of vitamin E and selenium deficient rats has shown that adriamycin clearly stimulates lipid peroxidation in these animals. The degeneration of heart muscle often seen as a side effect of adriamycin use may therefore be caused by the peroxidative damage preventable by higher levels of vitamin E and selenium.

Research on vitamin K investigates the mechanism of vitamin K on protein carboxylation and the mechanism by which calcium is required in the formation of protein phospholipid with vitamin K dependent plasma proteins.

Research on the water soluble vitamins emphasize the mechanisms and metabolism of vitamin C, niacin, thiamin, folic acid, B₆, and B₁₂. Vitamin C as an antioxidant to inhibit intracellular oxidations and the accumulation of possibly toxic oxidized products is being investigated in terms of the prevention of retinal degeneration and formation of lens opacities or cataracts.

Folate is one B vitamin that received a great deal of research attention. Studies on the biochemical-genetic regulation of essential folate pathways in cultural human cells have detected 9 of the 15 major folate pathway enzymes in crude extracts of cultured skin fibroblasts, peripheral blood lymphoblasts, and in amniotic fluid cells. Skin fibroblasts from patients with inborn errors of folate metabolism are being studied in order to understand the biochemical changes in methylene tetrahydrofolate deficiency and dihydrofolate reductase deficiency. Investigators have found that in the presence of normal methionine synthetase activity, the rate of synthesis of methionine from homocystine is a function of 5,10-methylene tetrahydrofolate reductase activity, and that the measurement of the methionine biosynthesis capacity of cells deficient in this enzyme accurately reflects the clinical status of the patient from which the cells were derived. The enzymes, dimethylglycine dehydrogenase and sarcosine dehydrogenase, appear to be the folate binding proteins of the mitochondria, while a high molecular weight folate binding protein containing bound tetrahydropterol pentaglutamate has been purified from the rat liver cytosol.

Dietary folates that exist primarily as pteroylpolyglutamates are absorbed in the jejunum by hydrolysis and subsequent intestinal transport of pteroylmonoglytanyl folate. The intestinal mucosa enzyme, folate conjugase is required for this transformation.

The requirement for folate in pregnancy is an important research focus since a marginal deficiency of the vitamin may have an adverse effect on folic acid status and growth of the newborn. An animal model of marginal folate deficiency in the cebus monkey will be used to compare the sequential appearance of any clinical or biochemical signs of folic acid deficiency in the mother and the neonate, to compare the folic acid status of the mother with the infant, and to ultimately estimate the folic acid requirements for pregnancy and lactation in the cebus monkey.

An important factor that enhances folate uptake by intestinal cells has been discovered in human milk, while a receptor protein that binds the folate has been isolated from intestinal cell extracts. These findings imply that protein-mediated folate absorption occurs in infants. In addition, studies have shown that the uptake of radioactive free folate is greatly enhanced by the saturation of breast milk with nonradioactive folate, suggesting a complicated binding and uptake mechanism for folate.

Research suggests that approximately 10 percent of congenital malformations in phenytoin-treated epileptics may be induced by a decrease in the availability of folate. This effect has been shown to be species specific in that oral administration of phenytoin caused reduced levels of plasma folate in man and mice, but not in rats or guinea pigs. Altered folate metabolism is also implicated in the pathogenesis of Martin-Bell-Fragile X syndrome; an X linked recessive pattern manifested as mental retardation.

Studies of folate depletion in normal and SV40-transformed human fibroblasts have shown that after 72 hours the transformed cells contained 3 to 10 times more polyglutamate than the normal cells, although the growth rates for the normal and transformed cells are similar. Inhibition of polyglutamate formation therefore may be an important potential target for chemotherapy. A folic acid antagonist, "x-methyl folic" acid that contains four more carbons than folic acid has been identified and could possibly be used as an antitumor agent in methotrexate resistant cancer patients.

Studies in rats attempt to determine the levels of S-adenosyl methionine and S-adenosyl homocysteine in the brains of rats fed diets lacking in B₁₂ (cobalamin), folate, and methionine. Levels do not appear to be affected unless the animals are treated with broad spectrum antibiotics when methotrexate is given to induce methyl deficiencies; none of the macromolecular methyltransferase enzymes or reaction products are affected.

Cobalamin deficiency, induced in the fruit bat model, appears similar to human pernicious anemia characterized by neuropathy but without hematologic complications. This model seeks to elucidate the metabolic role of cobalamin in nervous and other tissues and its interactions with folate. Cobalamin appears to enhance immunoglobulin production and release through IgG, as well as protein synthesis in normal and deficient human lymphocytes. This effect was enhanced by cobalamin per unit cell.

Niacin is present in foods chiefly as pyridine nucleotides. Metabolic studies have shown that nicotinamide is absorbed very rapidly by passive diffusion, while nicotinic acid is transported more slowly by facilitated diffusion with a greater proportion retained in the intestine and converted to nicotinamide adenine dinucleotide (NAD). Prior to absorption, NAD is largely converted to niacinamide through the actions of pyrophosphatase, phosphatase and glycohydrolase.

Studies are under way on thiamine's role in the function of the central nervous system. One research effort is concerned with the role of thiamine in neurotransmission and the mechanism of the demonstrated central

nervous system dysfunction in early stages of thiamine deficiency. The neurodegenerative condition known as Leigh's disease appears to be characterized by a disordered metabolism of thiamine-phosphate-esters in the brain. Investigators are attempting to purify cerebral thiamine-diphosphatase (TDP) and are measuring the cerebral synthesis of thiamine-triphosphate (TTP). TTP synthesis is blocked by an unknown factor found in urine of patients with Leigh's disease. In addition, studies are also investigating the interaction of thiamine pyrophosphate and branched chain ketoacid-dehydrogenase (BCKD). Thiamin appears to function at the site of enzymatic activity and produces a conformational change in BCKD that renders the complex more stable.

Biotin-responsive multiple carboxylase deficiency, a genetic disorder, can be prevented in utero by the administration of 10 mg. biotin per day to the mother during the last trimester of pregnancy. Thus, prenatal metabolic therapy of this enzymatic defect was successful by the oral administration of biotin to the mother during pregnancy which led to increased levels of biotin in cord blood and prevented the onset of profound biochemical and clinical abnormalities in the child.

A study on the special nutritional needs, including the need for vitamins, of the elderly is examining the nutritional status of 270 healthy individuals 60 years of age and older in an attempt to determine if illness is a consequence of subclinical malnutrition in healthy people and if nutritional deficiencies correlate with the decreasing ability to resist disease with age. Data gathered thus far show that the diets are generally adequate, except for the calcium and vitamin D intake of the women. Fifty-four percent of the women consume less than the RDA for vitamin D and their blood levels are low. In terms of vitamin C status, less than 2 percent of the individuals appear to be in danger of developing clinical deficiencies. The men, however, appear to need twice as much of the vitamin as the women in order to maintain optimal blood levels. Megavitamins have been shown to have little effect on immunological functions.

Behavioral Studies in Nutrition

The motivating forces controlling food selection and food intake are diverse. The physiological factors of taste, smell, gastric and humoral responses to certain foods are often influenced by social, cultural and religious values, as well as by learned habitual behaviors. Studies attempt to define the exact role of these values and behaviors on influencing food preferences and aversions, as well as define the influence of dietary intake on subsequent behavior. In FY 1982, NHLBI, NIADDK, DRR, NICHD, NINCDS, NCI, and NIA supported \$29,979,000 or 21 percent of total nutrition research expenditures for studies in this area.

Studies on the neurophysiology of learned ingestive behaviors examine the neuroanatomical and neurophysiological integrations at the level of the neuron and synapse. For example, a "wiring diagram" describing the connection of motor neurons that explains swallowing behavior has been developed. The relationship of changes in feeding behaviors to fundamental structures and functions of neurons is being further defined in animals.

Another study examines the effect of angiotensin and other chemicals injected into various parts of the brain on drinking and feeding behaviors. The receptor site within the brain for the dipsogenic action of angiotensin is being sought, with particular attention paid to the subfornical organ. Antidipsogens (prostaglandin E and substance P) are also under investigation for their selective competitive interaction with the dipsogenic action of angiotensin. The hypothesis that sodium appetite is aroused by a synergistic effect of angiotensin and aldosterone is another area of research interest.

In order to examine the chemical controls of food intake, physiological doses of catecholamines are being examined for their role in adrenergic mechanisms that either arouse or suppress the brain mechanism for feeding behavior.

Studies on the neuroanatomical connections from the viscera (especially esophagus and gut) to the brain attempt to describe the electrophysiological circuit activity from the central gray matter to the lateral parts of the brain that affect food intake. Many of these circuits appear to be of a reciprocal inhibitory nature, while connections to the limbic brain areas may be important for the emotional activity associated with eating. Studies of the hypothalamus and other parts of the midbrain indicate that neuroendocrine cells, in particular, change their activity with changes in the chemical and electrical surroundings. Chemical changes, especially of glucose and salt concentrations in the circulating blood, appear to affect the electrophysiological activity in certain areas of the brain; specific concentrations are associated with increased food intake, while others are associated with a decrease.

Studies carried out at the Regional Primate Research Center investigate the role of peptide hormones in the control of food intake and body weight in the baboon (Papio cynocephalus). Small amounts of insulin infusion into the cerebrospinal fluid appears to have a negative feedback control to the brain for food intake. The decrease of food intake and body weight is dose dependent. Studies to define the mechanisms for regulating eating behaviors and energy expenditure are also under way in rhesus monkeys (Macaca mulatta).

The ontogeny of drinking and feeding behavior is also being studied in suckling and weaning rats in order to describe the chronology of the physiological controls for each behavior as the animal matures. Studies of the glucostatic mechanisms for controlling suckling and nibbling latencies of rat pups have shown that suckling does not come under glucostatic control until the time of weaning at approximately 24 days, while nibbling behaviors come under glucostatic control at 21 days. These findings indicate that by day 21, rat pups have developed a specific appetite for carbohydrate and when challenged with a glucoprivic agent, their feeding behavior is directed towards a food source high in carbohydrate.

Another investigation in rats on the physiological basis of weaning indicates that elimination of the surges of thyroxine and corticosterone

hormones that appear just before weaning delays its onset. However, early treatment with either thyroxine or corticosterone do not appear to cause early weaning. Neither hormone therefore is the trigger for weaning but rather plays a permissive role.

Investigators have found that emetic areas of the brain stem mediate the acquisition and extension of conditioned taste aversions. It appears that olfaction is involved in both food selection and peripheral defense. Odor-taste interactions during flavor conditioning are being studied in terms of illness induced food aversions. Odors, when presented in conjunction with taste, become strongly associated with a food if ingestion of the food is followed by an illness. This phenomenon of potentiation is being studied and is known to be related specifically to feeding behavior. Potentiating odor-taste interactions do not occur if shock reinforcement is used. It appears that taste cues can index odor cues in memory as food-related stimuli. Lesions of the taste cortical area of the brain produce very specific disruptions in taste aversion conditioning, but do not affect odor illness conditioning or conditioning of taste potentiated odor aversions. The vagus nerve also plays different roles in flavor conditioning with vagotomized rats failing to acquire normal aversions--either taste, odor or potentiated odor--when the illness induced agent is a gastric irritant. Thus, severing the vagus nerve seems to eliminate an important component of the conditioned emetic response.

The Communicative Disorders Program supports basic studies of the neurological mechanisms of taste in a variety of animal models, i.e., rat, hamster, sheep, gerbil and dog. X-ray crystallography is used to study the biomedical models of sweet taste. This program also supports human clinical studies through the Chemosensory Clinical Research Centers on the relationship of taste to diseases such as diabetes, obesity, renal disease, and radiation-induced illnesses.

A number of studies investigate the role of specific nutrients or nutritional status on behaviors. Of special significance are the studies on nutrition, neurotransmitters, and behavior in terms of the effect of specific dietary nutrients on the levels of neurotransmitter precursors in the brain and in turn the amount of neurotransmitters formed. Tryptophan is converted into serotonin; tyrosine is converted into dopamine, norepinephrine and epinephrine; and choline is converted into acetylcholine. These end products are all neurotransmitters. Research has shown that an increase in the brain level of the precursor enhances the synthesis of the corresponding neurotransmitter, which in turn increases the transmission of signals from the neuron to the cell it innervates. Tyrosine and choline, however, amplify neurotransmission selectively, increasing it at some synapses but not at others.

It is known that the proportion of protein and carbohydrate in the diet influences the conversion of tryptophan to serotonin, the neurotransmitter which delivers signals to scattered groups of neurons that control sleep, mood and appetite. Data indicate that feeding animals large amounts of protein causes a reduction of brain levels of tryptophan and the synthesis of serotonin. This reduction is mediated by the ratio of plasma tryptophan

to five other amino acids in plasma (tyrosine, phenylalanine, leucine, isoleucine, and valine), which compete for a carrier molecule needed to transport them across the blood-brain barrier. Because most proteins contain less tryptophan than the other five amino acids, a high protein meal reduces the ratio of tryptophan to the competing amino acids in the plasma. A high carbohydrate meal, on the other hand, has the opposite effect, as the insulin which is secreted reduces the plasma levels of the other amino acids more than the level of tryptophan. The serotonin-releasing neurons in the brain serve as sensors of the ratio of tryptophan to the other amino acids in the plasma; serotonin release increases after a carbohydrate meal and is reduced after a high protein meal. Thus, eating a meal rich in carbohydrate and poor in protein generates a neurochemical change--namely increased serotonin synthesis that causes the animal to reduce its intake of carbohydrate but not of protein.

Most people appear to need 6-12 grams of carbohydrate to elicit the secretion of sufficient insulin to lower plasma levels of the large neutral amino acids (LNAA), while 25 grams are needed to raise the plasma tryptophan/LNAA ratio and thus enhance brain serotonin synthesis. Obese people may suffer from a disturbance of this remarkable feedback mechanism that links nutritional, metabolic, and neurochemical and behavioral systems.

The clinical application of research on nutrient-neurotransmitter relationships has been particularly relevant to treating patients with tardive dyskinesia (the impaired ability of voluntary movement seen in the elderly, induced by long-term use of certain drugs such as tranquilizers), high blood pressure, depression, Parkinson's disease, and other disorders. In patients with tardive dyskinesia, choline and lecithin have been shown to effectively prevent the side effects seen with the prolonged administration of antipsychotic drugs. The neurons that suppress the symptoms of the disease are apparently sensitive to the additional supply of choline. Lecithin therapy may also prove useful in treating memory disorders associated with old age.

Tyrosine in its role as precursor of norepinephrine may be an effective antihypertensive agent. The possible therapeutic value of tyrosine for depression is also under investigation. Many psychiatrists believe that depression reflects the inadequate neurotransmission mediated by norepinephrine and possibly serotonin. Other studies have shown that the administration of 100 mg/kg/day of tyrosine to patients with Parkinson's disease enhances catecholamine release from frequently firing catecholaminergic neurons. Studies in rats have shown that 100 or 150 mg/kg of tyrosine in a single oral dose significantly increases urinary levels of all catecholamines and their metabolites for approximately 2 hours. Thus, in humans as well as in rats, tyrosine may enhance catecholamine release from both central and peripheral tissues.

Another study in rats has shown that relatively small variations in the protein/carbohydrate ratio of a diet given for short periods of time significantly altered the motor activity of rats; an increase in the ratio made the rats more continuously active. Thus, changes in the diet can significantly alter behavior.

A number of investigations are under way to examine the behavioral effects of protein calorie malnutrition, iron deficiency, zinc deficiency, and heavy metal toxicity. Studies on the development of the central nervous system and the resultant behavior in rats fed protein deficient diets (8 percent versus 25 percent in controls) reveal a marked increase in the regional concentrations of cerebral norepinephrine, altered hippocampal electrical activity with increased theta activity, hyperactivity to aversive stimuli such as electric shock and increased copulatory activity. In addition, low protein diets fed prior to conception produce substantial changes in the physiological properties of spontaneously active cells in the frontal neocortex. The same protein malnutrition effect was also apparent with a low protein diet given immediately at birth following a normal gestation. Thus, the period of vulnerability to developmental malnutrition extends into the lactational period. It is important also to note that a normal diet given to rats after gestation does not reverse the effects of gestational protein malnutrition.

Other scientists attempt to separate the effect of malnutrition and environmental variables on behaviors. Malnourished rat pups, mother deprived and reared by nonlactating aunts, were found to be slower than controls to habituate to open field testing. Environmental effects, such as handling were found to produce behavioral effects as strong as those of undernutrition. This study also noted that malnourished rats benefit less from environmental enrichment than normal animals.

Studies on the effect of zinc deficiency on exploratory behaviors in young monkeys include tests of climbing, exploration, manual dexterity, oddity learning, social motivation and behavior, level of arousal, and organization of behavior. Results indicate that offspring of zinc deprived mothers had less exploratory behavior activities in the absence of any overall alteration in locomotor activity or arousal levels. Zinc deprived offspring did not appear to be deficient in learning spatial delayed responses and brightness discrimination tasks, although the error patterns in these animals were similar to the type common in monkeys with brain damage due to prenatal anoxia or developmental exposure to toxins.

Another study on the behavioral effects of lead exposure from dietary, maternal, and airborne sources are being assessed through neuropsychological performance tests of infants and school children with high and low levels of cord-blood and dentine lead, respectively. Initial results indicate that children's behavioral outcome measures were dose related to lead, with the poorest performance associated with the highest levels of dentine lead. Elevated dentine lead levels increase a child's risk of needing daily remedial academic aid; 50 percent of the children above the 90th percentile of lead distribution received remedial aid versus 16.9 percent of the children below the 90th percentile. The children's IQ scores (WISC-R) appeared to fall short of expected IQ scores with elevated levels of dentine lead (20 parts per million).

Nutrition, behavior, and changes with age is another area of investigation. Research has shown that moderate to severe undernutrition after weaning extends a rat's lifespan by as much as 50 to 100 percent. A

study is under way to study sensory motor and cognitive function (learning and memory) in such rats whose lifespan has been prolonged by undernutrition. In addition, changes in learning, and memory storage and retrieval are being analyzed in the normal rat with age. Individual differences between the normal rat and an undernourished rat with age will be compared in terms of the rate of loss of both sensory motor and cognitive function.

A study on gustatory and olfactory quality changes with age has shown that older subjects have a lower taste and smell acuity. Thresholds for taste are increased by a factor of 2.5 for amino acids and 2.7 for sweeteners. This decreased acuity for sweeteners can lead to weight gain with addition of nutritive sweeteners, and adverse dose-related biological effects with artificial sweeteners. The decrease in olfactory acuity is greater than that for taste, with olfactory thresholds for a series of artificial food flavors shown to be 11 times greater in the elderly than in the young. The data show that in addition to the age-related losses in thresholds, perception of the growth in intensity with concentration and discrimination is also reduced. The ability to discriminate among odors is also greatly reduced.

Sensory losses do not appear to be uniform across stimuli; for example, the odor of 2 methoxy 3 isobutyl pyrazine (green pepper) was discriminated from the alkyl pyrazines, but alkyl pyrazines were not discriminated from each other. Also, of the L amino acids, more age-related taste loss appeared for L-glutamic acid and L-aspartic acid.

Social factors and health changes with age also affect dietary habits. Patterns of carbohydrate consumption of adults aged 65 to 74 years have been analyzed in terms of living arrangements, i.e., living alone, living with a spouse only, living with a spouse and children, living with a non-relative, living with a parent or other relative, and single head of a household. Carbohydrate intake as a proportion of total calories, number of carbohydrate servings per day or proportion from complex carbohydrates were consistent across living arrangements, except for single heads of households and nonmarried persons living with a relative where complex carbohydrate use seemed lower. However, calories from complex carbohydrates were greater for the older adults than for younger adults, regardless of living arrangements. Thus, the elderly appear to rely on fruits, vegetables, breads and cereals as carbohydrate sources. Another study will examine how dietary intake and habits are affected when adults 62 years of age and older are moved from age-dispersed to age-segregated housing. The study will identify those persons whose eating is most responsive to external stimuli in order to identify those individuals most at risk for nutritional deficiencies when environmental changes occur. Social networks, and factors determining experienced stress and effectiveness of coping in older persons will be examined in relation to eating patterns.

Another epidemiological study that examines the effect of socialization and modernization on a specific population's nutritional status is studying Samoans who move to California. This study indicates that they undergo a more significant increase in weight and cardiovascular risk than those Samoans who move to Hawaii. This appears to be due to

an increased level of industrialization, rather than purely genetic risk factors. To further explore the effect of modernization on several measures of cardiovascular aging, research in a Tibetan population will examine the influence of attitude, activity, the timing of events in the life cycle, and other environmental variables on biological aging in infants, adolescents, and adults.

The effects of cultural, social and economic factors on trends in breast feeding are being investigated in the Pima Indians, the Negev Bedouins and middle class black and white mothers in the U.S. A pilot study conducted in the District of Columbia revealed the incidence of breast feeding in an urban hospital at 75 percent. Of those women who breast fed their infants, 70 percent were white, 86 percent were married, highly educated (15.8 mean years), and older (mean age 29). Of the women choosing to bottle feed, 80 percent were black, 50 percent were unmarried, the average age was 25 years and the average number of years of schooling was 13.5. The increase in breast feeding in the U.S. has been most pronounced among white women, primarily of the higher socioeconomic groups. The duration of breast feeding also seems to be on the upswing, especially among the upper socioeconomic status white women. This pilot study also revealed the following factors as influencing the women's rationale for weaning before 4 months: insufficient milk, baby rejected the breast, and mother's return to work. In addition, 57 percent of the short-term breast feeders used formula in the first month postpartum with the claim of insufficient milk as the primary reason for introducing the formula.

Studies have reported a strong "within culture" correlation between food attitudes of parents and their children, especially in the area of disgust and contamination sensitivity. It seems that the child's conception of food develops in the following sequence: children less than 2.5 years reject only foods that are distasteful; later, they reject foods because of anticipated harm or danger; and rejections due to disgust appear last. The rejection of good foods due to contact with offensive substances--a hallmark of disgust--does not appear until 6 years of age. The youngest children believe that something that is bad for them will taste bad.

Data on the child malnutrition rates in Papua, New Guinea have shown that these rates follow cultural rather than environmental boundaries. The highest reported rates in the Sudest Island area of New Guinea correspond with the area where traditional proscriptions against feeding young children animal protein foods are scrupulously followed. These proscriptions may be a cultural adaptation to the local environment of hyperendemic malaria, a major cause of child mortality.

Various social, familial, and personality factors that influence persons who develop anorexia nervosa are being examined. Data indicate that anorectics have a phobia of ingesting food and gaining weight, maintain an avid interest or even an obsession with food and flavors, and do not report a loss of appetite or hunger. A study is under way to examine the role of standards of physical attractiveness and ideal body physique in anorectics and normal weight adolescent subjects with no history of being significantly underweight or overweight. Significant sex differences have been seen in the perceptions of normal weight. The normal weight

females exhibited a desire to be thinner even though their present body weight appeared normal, and they expressed a significant preoccupation with food and dieting. The males, however, reported their ideal weight as consistent with their present weight or even higher. The females' idea of physical attractiveness followed a norm of extreme slenderness.

Many studies investigate various methods to change health behaviors, particularly in terms of diets associated with different diseases. The Stanford Heart Disease Prevention Program continues its communitywide programs for primary prevention of cardiovascular disease through development and distribution of new brochures on blood pressure control, brief television spots on weight control, and a multimedia smoking cessation program. Changes in the risk factors for cardiovascular disease, including dietary habits, are being assessed in 1,400 subjects of the control and intervention communities. The Minnesota Heart Health Program and the Pawtucket Heart Health Program are other community based demonstration studies investigating the influence of community intervention efforts on changes in health behaviors associated with cardiovascular risk.

Additional types of demonstration projects are designed to modify a family's risk for cardiovascular disease; to explore the possibility that dietary change and/or relaxation training will reduce the need for medication in hypertensive individuals; to determine the medical cost-effectiveness of specific interventions designed to improve blood pressure control in defined populations; and to assess the effect of educational behavioral programs directed at high risk patients and families.

Changes in eating behaviors, particularly anorexia nervosa and taste aversions, are common problems in cancer patients. One hypothesis being tested is that anorexia, associated with neoplastic disease, is secondary to peripheral metabolic changes induced by the presence of a tumor.

Research has shown that in neoplastic disease the increase in nonesterified fatty acids displace tryptophan from albumin making it more available for entry across the blood-brain barrier. Therefore, by manipulating the plasma concentrations of free or total tryptophan, or other competing large neutral amino acids, or by administering serotonin antagonists, physicians may prevent the development of anorexia. Another study seeks to determine whether taste aversion problems found in clinical radiation and gastrointestinal chemotherapy result from induced taste aversion. The effectiveness of progressive muscle relaxation (PMR) in reducing psychological anxiety, nausea, and vomiting in two groups of cancer patients is also being examined in terms of the effect on nutritional status.

Studies on nutrition and behavior in relation to treatment for obesity examine various behavioral changes necessary for weight reduction. In a home based behavioral program for obese children, parents are being trained to model appropriate eating or exercise behaviors for their overweight child to imitate. Results of the study indicate a much greater success rate for children at maintaining normal weight if their parents were actively involved in the weight reduction program. This study will also examine the relative importance of eating control versus exercise in the management of childhood obesity.

Training children to eat slowly and pause more frequently between bites is also being examined as an effective method to achieve long-term behavioral changes related to preventing the onset of obesity. Also, teaching preschool children positive health and dietary behaviors has been shown to initiate such behaviors, especially if the information and materials being used are fun, age-relevant, and usable by the child.

The effect of dietary intervention on behavioral changes in children with the various inborn errors of metabolism is also being investigated. For example, studies have shown significant increases in the mean full scale IQ scores of children with phenylketonuria (PKU) who remain on a low phenylalanine diet after the age of 6. Achievement tests for spelling and reading also revealed small but significant differences in favor of those who remained on the diet at 8 years of age.

Results of rat studies on the cause of brain damage in phenylketonuria have shown that elevated levels of phenylacetate in the rapidly growing brain induce biochemical, structural, and behavioral deficits that simulate experimental hyperphenylalaninemia. The deficit in cognitive function seen with this metabolic error may be related to deficient synaptic development or to interference with acetyl CoA synthesis or utilization. Another animal model of hyperphenylalaninemic rats also has shown impaired latent learning and observational learning.

A study of seven girls, symptomatic heterozygotes for ornithine transcarbamylase deficiency, involved dietary treatment combining protein restriction (1-1.5 g/kg/day) with arginine supplements (1 mmol/kg), benzoate (250 mg/kg) and/or phenylacetate. As a result of the treatment, one girl showed a decrease in plasma ammonium levels toward normal, improvement in hyperactivity and irritability behaviors, and an increase in her IQ score. A relationship appeared to exist between the magnitude of hyperammonemia, the duration of coma, and neurodevelopmental progress.

A high incidence of migraine headaches and protein intolerance manifested by cyclical vomiting, particularly among heterozygote women, has been detected in families with evidence of ornithine transcarbamylase deficiency. Other studies of urea cycle enzyme defects have shown that heterozygotes, although having full scale IQ scores within the normal range, did appear to have significantly larger verbal-performance IQ differences--an indicator of cortical dysfunction. Perceptual and motor function changes were studied in heterozygotes following an alanine challenge in order to evaluate the effect of asymptomatic hyperammonemia on cortical dysfunction. No acute changes were noted with modest hyperammonemia.

A pilot study of voluntary protein intake of asymptomatic heterozygotes for urea cycle enzyme deficiencies suggest that these individuals may, in fact, unknowingly restrict their protein intake. The protein intake for 3 days for the heterozygote women averaged 0.6 ± 0.1 g/kg/day while that of their unaffected spouse average 1.2 ± 0.3 g/kg/day.

Elevated plasma ammonium levels during the first 2 months of life have also been found in more than 50 percent of the low-birth-weight infants. Arginine supplementation (1-2 mmol/kg/day) beginning in the first 2 weeks of

life was found to be effective in lowering plasma ammonium levels to normal.

Studies of the possible long-term effects of this clinically asymptomatic hyperammonemia on neurological integrity of the infant include measures of auditory habituation and primitive reflex profiles. Interim results from the Bailey Infant Development Scales indicate no significant differences in auditory habituation, primitive reflex profiles or IQ between infants having normal ammonium levels, hyperammonemia-arginine treatments, and hyperammonemia without treatment.

Child and Infant Nutrition

Genetics and the effect of environmental influences, such as nutrition, play a major role in the proper growth and development of infants and children. In FY 1982, NICHD, NHLBI, DRR, NIADDK, NIAID, NCI, NIDR, NINCDS, NIEHS, and NIGMS supported research in child and infant nutrition for a total of \$24,197,000 or 17 percent of the total nutrition expenditures.

In order to clearly understand growth and development throughout the life cycle and under certain conditions, research continues to better define the nutrient requirements of normal term infants at birth and during the first year of life, and the requirements of the low-birth-weight premature infant and growth retarded infant. The requirements for protein and energy, vitamins, minerals and trace elements for maintaining acceptable rates of extrauterine growth and development must be ascertained.

In terms of establishing the nitrogen requirement of infants, some metabolic studies have raised serious questions about the validity of the nitrogen balance technique. Other studies continue to investigate the influence of zinc on fetal and neonatal development in normal infants and those with failure to thrive, as well as the bioavailability of zinc added to breast milk versus bovine milk. Low zinc content in breast milk was shown to result in acrodermatitis and hypozincemia in 9-week-old premature breast fed infants; these symptoms were alleviated within seven days with oral zinc supplementation. Zinc secretion into breast milk appears to be a controlled process independent of zinc intake and serum levels. Additional studies have shown that a low zinc intake decreases appetite and can limit skeletal growth rates of rapidly growing young children.

Data from animal studies indicate that rat pups from mothers made zinc deficient during the last week of gestation and the following 18 days of lactation develop more dental caries than controls. In other studies on the development of teeth and caries resistance, the role of fluoride as well as the role of vitamin A in the calcification of teeth and bones is being investigated.

Additional attempts to determine specific nutritional demands and to uncover the possible role of nutrition before and immediately after birth has led to exploring the environment of the fetus and neonate. For example, studies to devise the appropriate nutrient therapy for the

low-birth-weight infant involve controlling the complex functions of the placenta for as long as several months. Investigations are under way on total parenteral and enteral nutrition, metabolic balance and calorimetry, and research on immunological and nutrient composition of colostrum and human milk from mothers who deliver at various gestational ages.

Research has shown different rates of growth in the low-birth-weight infants by adjusting the caloric and nutrient density of the diet. A 3-year, carefully controlled clinical study, initiated in FY 1982, is designed to compare growth and development of low-birth-weight infants fed isocaloric and isonitrogenous preparations of human milk and formula. Physical growth, immunological development, and gastrointestinal function of these high risk infants will be evaluated in response to the biologically active components believed to be present in breast milk.

The appropriate nutritional therapy for the premature infant must take into account the immaturity of various enzyme and transport systems, since these systems become saturated at nutrient concentrations that vary directly with gestational age. A high rate of physical growth while keeping the circulating substrates and metabolites within acceptable ranges must be maintained. Investigators have found that premature infants lack the enzyme capability to manufacture tyrosine, arginine, cysteine and cystine, as well as taurine and histidine. These six amino acids, in addition to the eight required by adults, are therefore essential to the premature infant. When the concentration of any of these essential amino acids falls below a certain critical level, it becomes rate-limiting in terms of growth. Methionine intake has been shown to be limited with certain infant formulas; therefore, studies are measuring 3 methylhistidine excretion of infants fed soy formula diets supplemented with methionine.

In addition, the premature infant has minimal stores of carnitine which is important for fatty acid transport across the mitochondrial membrane; hence, the enzyme activity responsible for its synthesis is probably low. Since all soy based infant formulas are devoid of carnitine, the nutritional management of these infants can become complex. Studies are also under way on the effect of medium chain tryglycerides and taurine on fat absorption in the low-birth-weight infant.

The proper protein intake for premature infants has yet to be resolved. Some investigators believe that intakes in the range of 2.5 to 3.0 g/kg/day (two to three times that supplied by human milk) are needed to maintain a growth rate comparable to a fetus of a similar age. Therefore, supplementary cow's milk protein would be needed. Other investigators still believe that the unique composition of human milk makes it ideally suited for the nourishment of these infants.

Studies on infant feeding have shown that infants during the first few days of life prefer sweeter formula feedings (i.e., sucrose over lactose and fructose over glucose). One study of normal female infants from 8 to 112 days of age found that infants fed the sucrose-containing formula had greater mean energy intake per unit of body weight and greater mean gains in weight than those infants fed polydose (a cornstarch hydrolysate of bland taste). Results from this study suggest that differences in the

type of carbohydrate in an infant formula influence food consumption; however, with longer term feeding (>20 to 28 days), adaptation to the formula might occur in that the infant may adjust formula consumption to meet energy needs independent of the type of carbohydrate in the formula. The possibility that differences in sweetness may lead to differences in weight gain and/or body composition requires careful research assessment.

The development of the digestive function in the newborn is another important area of research. The newborn has a limited supply of energy reserves in the form of body fat, and its intestinal tract must adapt very quickly to support all of the infant's energy and growth needs. A complex series of secretions released from the oral cavity, stomach, and intestine play a critical role in digestion and absorption of fats, complex carbohydrates, and protein. Several studies are under way to characterize the progression of digestive processes that are turned on near the time of birth and thereafter. In terms of fat absorption, an animal model has been developed to analyze bile acid secretion in the newborn, while another study investigates the role of fat ingesting enzymes secreted in the mouth and stomach. Research has shown that lingual lipase is a major contributor to fat digestion throughout postnatal development.

Studies are also under way to identify the numerous maternal factors that influence the mechanisms of fetal gastrointestinal development; these factors include the mother's nutritional status before and during pregnancy, maternal genetic makeup and hormonal status. Two systems have been developed to study the mechanisms controlling morphogenesis of the small intestine.

In order to explore the premise that hippocampal and cerebral development in the neonate and differentiation of hypothalamic mechanisms at this critical time could result in deficits in later reproductive function and in learning and activity, the effects of polychlorinated biphenyl (PCB) exposure during early postnatal development is being investigated in the rat. Lactating rats are exposed to three different doses of PCB immediately after the birth of their offspring in order to investigate the PCB's effect on reproductive ability, mating behavior, and activity learning in the female offspring when they reach adulthood. Other research on nutrition and neurological development is investigating whether early undernutrition causes abnormalities in the synthesis or structure of gangliosides and glycoproteins in the synaptic plasma membranes (SPM). Data have shown that the offspring of rats fed either a protein-calorie deficient diet or a protein-deficient diet during lactation had a significant deficit of SPMs as assessed by SPM protein content. This deficit was greater in the hippocampus and forebrain than in the cortex or cerebellum.

The composition of human milk and the special functions of its components is an important research area relevant to infant nutrition. Special analytical procedures are being used to determine the full range of lipids present in the milk throughout the lactation period, as a result of maternal age and diet. Trace elements, and amino acids and protein fractions of human milk and colostrum are also being evaluated. One project is evaluating the effect of medications used during labor and

delivery, as well as smoking and prescription drugs on the composition of milk.

Immunological properties of human milk are believed to make a major contribution to effective host resistance during infancy. Studies are under way to evaluate the functional properties of the lymphocytes and macrophages found in colostrum and milk. Investigators have determined that human milk contains high concentrations of lactoferrin and lysozyme (two soluble proteins that inhibit bacterial growth in the gastrointestinal tract of human newborns; lactoferrin by binding the iron required for bacterial growth and lysozyme by bacterial lysis); secretory immunoglobins (IgA) that coat the newborn infants' intestinal lining and are directed against bacterial antigens to which the mother and infant are exposed; macrophages, T lymphocytes and B lymphocytes that appear to play a role in neutralizing the effects of viruses, bacteria, bacterial toxins, and other foreign antigens including allergenic food antigens; and several growth factors (mitogens) that stimulate DNA synthesis and induce divisions in cells grown in culture. Breast milk mitogenic activity is concentration dependent, is greatest early in lactation, and may play an important role in the growth of intestinal mucosa cells.

In order to understand the immunologic responses to different products and regimens proposed for feeding infants when mother's milk is not available, a longitudinal study was carried out on the levels of specific antibodies in infants fed cow milk and soybean proteins. Data from the study reveal that the continuation of cow milk feeding beyond 112 days causes the mean values for the levels of antibodies to milk protein to increase, and perhaps reach a plateau by the age of 196 days (6-1/2 months).

This research indicates that the magnitude of the antibody response to milk protein is affected by the nature of the food protein, the concentration in the product, and the heat treatment applied during the processing. In addition, the type of initial feeding appears to influence the antibody response to milk products introduced later; i.e., the antibody response to pasteurized cow milk introduced after initial soy feeding was significantly greater than when introduced after cow milk feeding. This study reveals that soy products fed from birth to 4 months of age did not prevent a brisk antibody response to cow milk introduced later in infancy. Thus, from an immunological standpoint, when mother's milk is not obtainable the preferred substitute formula for infants appears to be a heat-treated lower protein, cow milk base product rather than a soy product.

The increased awareness of the nutritional value of breast milk has stimulated the establishment of a number of milk banks in the U.S. and throughout the world. Such milk banks serve to supply milk for clinical care and clinical investigations on infant nutrition, to bank milk for later feedings to normal infants, and to allow mothers to store milk for feeding her infant when she is unable to breast feed. A workshop, "Breastmilk Banking: Current Status and Future Needs," was held in FY 1982 in order to compile information on current milk banking techniques and to project future needs for banked milk as well as potential future methodologies.

Research on human milk banking continues to investigate techniques of collection, fractionation, storage and distribution of human milk as well as the effects of maternal factors on breast milk composition. Preserving the viable immunologically active cells in human milk and colostrum involves determining methods of high temperature, short duration heat processing that destroys the bacterial and viral contaminants while at the same time leave intact the biologically active properties of the milk, i.e., the immunoglobins, lysozymes, lactoferrin and growth factors. Maternal factors such as age, nutritional status, smoking, diet and duration of lactation are investigated in terms of their effect on breast milk composition and volume.

In an attempt to understand the production of milk in the mammary gland and the biological basis for lactation failure, an animal model that isolates mammary end buds by microdissection has been developed and is now being used to evaluate the hormonal controls that govern the release of specific enzymes into the milk. Another system, an affinity chromatography system for isolating the estrogen receptors from mammary tissue, has also been developed and will be used to characterize the biological events of mammary development during the reproductive cycle.

Studies are under way on the physical and mental development of infants with various kinds of malnutrition including protein-calorie malnutrition, specific nutrient deficiencies and excesses (e.g., iron deficiency or lead excess), or malnutrition brought about by inborn errors of metabolism. Undernutrition often occurs in various disease conditions such as cancer, as well as with the inborn errors of metabolism such as phenylketonuria, galactosemia, homocystinuria, and other disorders of sulfur amino acid metabolism. Highlights of the research on the inborn errors of metabolism are described in detail as part of the special interest area on "Nutrition and Genetics."

Work on protein calorie malnutrition (PCM) in infants has revealed the existence of an intrinsic though reversible disorder of polymorphonuclear leukocyte motility with findings of diminished chemotaxis, increased cell adherence, activated cell morphology and unipolar distribution of surface adhesion sites with neutropenia. Such data suggest that the PCM child represents a new example of a leukocyte aggregation syndrome that may be caused by complement activation and sepsis.

A number of studies of pediatric patients carried out by the Clinical Nutrition Research Units involve the formulation and evaluation of various mixtures used for total parenteral nutrition (TPN). Examples of specific research include studies on the effect of cystine and taurine supplementation to TPN solutions in infants; the metabolic fate of intravenous fat emulsions; the effect of quantity and source of calories on nitrogen balance; net amino acid balance during TPN; hepatic dysfunction; the effect of amino acid infusions on plasma amino acid patterns; growth and metabolic variables of very low-birth-weight infants on combined enteral-parenteral feeding regimens; and the prospective evaluation of several modes of nutrition support (i.e., enteral, partial parenteral, peripheral nutrient infusion with enteral nutrition, and total parenteral nutrition) in children receiving multimodal treatment of stages II to IV Wilms' Tumors.

Additional research considers alterations in lipid metabolism in cystic fibrosis, irritable colon of childhood, optimal intakes of zinc and copper in pediatric patients, nutritional status assessment procedures, the use of 1,25 dihydroxyvitamin D₃ in steroid induced osteopenia, and the effect of chronic dialysis on vitamin and trace mineral hemostasis in children.

It appears that in children with moderate renal insufficiency, a restriction of dietary phosphorous increases the plasma concentrations of 1,25 dihydroxyvitamin D which reflects a reduction of and suppression of 25-hydroxyvitamin D-1 and hydroxylase activity. Additional studies in children show that oral phosphorous loading suppresses plasma levels of 1,25 dihydroxyvitamin D despite an increase in serum levels of parathyroid hormone. These findings together with animal data provide strong evidence that phosphorous intake plays an important role in the regulation of 1 α hydroxylase in the remaining functioning nephrons.

In studies of pediatric head trauma patients, the extent of hypermetabolism is being evaluated. Indices of hypermetabolism (oxygen consumption, nitrogen excretion, altered hormonal milieu) are being correlated with nutritional status, catecholamine levels, physiological reflections of increased sympathetic nervous system activity, and neurological outcome. It is hypothesized that a sustained elevation of catecholamines will be found after head trauma which mediates profound changes in metabolism and may impede neurologic recovery. Efforts are being undertaken to improve neurologic recovery after head injury by appropriate nutritional assessment and therapy.

Research on obesity in children examines the physiological effects of diet and exercise in obese children; behavioral precursors in infant obesity; early nutrition and the development of obesity; fat and fat-free body composition in children. In children with Chron's disease, usually manifested by growth retardation due to intestinal obstruction, abscess formation and decreased intestinal absorption, special diets administered to the children appears to increase their growth velocity.

Nutrition and Genetics

Research on genetics and nutrition include studies on inborn errors of metabolism; metabolic differences in nutrient requirements; chromosomal aberrations and determinations of cellular function, especially DNA repair mechanisms; and the effects of dietary intervention on inherited diseases or conditions. NHLBI, NICHD, NIADDK, NCI, DRR, NIEHS, NINCDS, NEI and NIA supported a total of \$18,946,000 or 13 percent of the total nutrition expenditures.

The study of genetic variants in man and in animal models helps to advance our understanding of both normal and abnormal biochemistry. The various inborn errors of metabolism under investigation include phenylketonuria, galactosemia, maple syrup urine disease, urea cycle enzyme deficiencies (isovaleric acidemia, hyperglycinemia, hyperargininemia, citrullinemia, methylmalonic aciduria, hyperornithinemia, hyperlysinemia), biotin responsive carboxylase deficiency, cystinosis, and Menkes' kinky hair syndrome. Research continues on the dietary manipulations often used to overcome or

bypass the enzymatic defects that characterize the inborn errors of metabolism.

Elimination diets have been shown to prevent the accumulation of nutrient substrates in metabolic pathways prior to the metabolic defect. For example, patients with hyperargininemia have shown a steady clinical improvement when treated with semisynthetic diets of N equivalent 0.6 gm/kg/day. In addition, preliminary findings from studies of gyrate atrophy of the choroid and retina suggest that controlling the blood level of ornithine through arginine deficient diets or pharmacologically through agents that increase excretion may modestly improve vision.

In an attempt to develop appropriate elimination diets for the treatment of familial hyperlysinemia, investigators have found that this inherited condition is caused by a deficiency in either one of the first two enzymes involved in the degradation of lysine. They have also initiated studies on the metabolism of pipecolic acid, an amino acid related to lysine and found to be elevated in patients with glutaricaciduria and pipecolic acidemia.

Other suggested treatments for various genetic disorders include using large quantities of vitamins to alter the decrease in cofactor affinity. For example, large quantities of pyridoxine are given to patients with pyridoxine-responsive seizure disorders or pyridoxine-responsive homocystinuria in order to overcome a decreased affinity of the apoenzymes (glutamate decarboxylase and cystathionine synthetase, respectively) for their vitamin B₆ cofactor. Similarly, treating patients having multiple carboxylase deficiency (propionyl CoA carboxylase and 3 methylcrotonyl CoA carboxylase) with large amounts of biotin has resulted in complete clinical recovery.

Increased dietary intake of the essential metabolites that lie in pathways beyond the deficient enzymatic reaction also seems to ameliorate some conditions. For instance, treating patients having Type I and Type III glycogen storage disease (GSD) with 150 percent of the daily glucose production as a glucose infusion significantly reduced glycine turnover rates; less glycine was needed for gluconeogenesis. This therapy may prevent the growth failure of GSD that is caused by the consumption of protein stores in a futile effort to synthesize glucose.

In patients having biopterin-deficient hyperphenylalaninemia (a variant form of PKU), providing 5-hydroxytryptophan, dihydroxyphenylalanine, tetrahydrobiopterin and biopterin supplements has been successful. This form of PKU is due to a deficiency of dihydropteridine reductase (DHPR), an enzyme that provides a reduced biopterin cofactor needed to convert phenylalanine to tyrosine and tyrosine to dihydroxyphenylalanine (DOPA), and tryptophan to 5-hydroxytryptophan. In other cases of PKU due to a deficiency of phenylalanine hydroxylase, the enzyme needed to convert phenylalanine to tyrosine, it appears that providing tyrosine helps to promote proper growth and development. Tyrosine is needed for the synthesis of thyroxine, melanin and catecholamines as well as for protein synthesis.

The low phenylalanine diet for the treatment of PKU appears to be the most successful regimen for this frequent disorder. An important research question being explored, however, is at what age can a low phenylalanine diet be replaced with a normal diet. Intellectual and perceptual skills have been assessed in two groups of children with PKU who at age 6 were randomly assigned to either a low phenylalanine diet or normal diet: mean full scale I.Q. scores differed significantly (103 for those on the low phenylalanine diet and 98 for those on a normal diet). Blood phenylalanine levels >20 mg/dl were associated with declining IQ scores, while values <20 mg/dl were associated with rising IQ scores. In terms of reading and spelling achievement, small but significant differences were found in favor of the diet continued at age 8, but not at ages 9 and 10.

Diet therapy provided to pregnant phenylketonuric mothers appears to have various outcomes in the child ranging from mental normality with no evidence of fetal effect to neonatal death due to congenital heart disease. Available data support initiation of therapy prior to conception for best results.

Another relevant aspect of this research deals with the neuropathological basis for cerebral dysfunction in PKU. It seems from rat studies that high levels of phenylacetate, a metabolic product of phenylalanine, causes a decreased brain weight and alterations in the dendritic branching of pyramidal neurons in certain regions of the brain. In an experimental model of PKU and hyperphenylalaninemia, the administration of phenylalanine alone or combined with d-methyl-phenylalanine is being examined in terms of the effect on protein metabolism (i.e., phosphorylation and synthesis). Results have shown that cyclic AMP dependent protein kinase is decreased in the brain and phosphorylation of a specific ribosomal protein is inherited under these conditions.

Diet therapy and management of the urea cycle enzymopathies are also being tested. These inborn errors of urea synthesis occur about once in 30,000 births with infants unable to manage nitrogen metabolism, and therefore to carry out the metabolic steps required for normal growth and development. Investigators have reported successful results with therapies that use alpha-keto analogs of amino acids to stimulate nitrogen waste excretion. The keto analogs serve as amine group receptors and thereby reduce the amount of nitrogen excreted as urea; the keto acid analogs are transformed into essential amino acids needed for protein synthesis. D-keto-isocaproic acid, and the keto analogs of valine, isoleucine, methionine, and phenylalanine are now being used in this dietary therapy. The use of alternative metabolic pathways for excretion of excess ammonia and other nitrogenous metabolites are also being investigated; e.g., hippuric acid, phenylacetylglutamine, arginine or other components of the urea cycle such as citrulline or argininosuccinic acid may serve as possible endpoint alternatives to urea. A significant decrease in ammonium levels has been shown in patients with urea cycle enzymopathies by the oral administration of sodium benzoate which conjugates with glycine to form hippuric acid, and administration of phenylacetic acid which combines with glutamine and is excreted as phenylacetylglutamine. Infants treated prospectively have the best outcome and appear to have normal intellectual development.

Many people who live in the Mediterranean basin or in the malarial belts of Africa and Asia suffer from chronic hemolytic anemias caused by shifts in the intracellular redox potential. High doses of vitamin C appear to be successful in the treatment of the chronic hemolytic anemia associated with glucose-6-phosphate dehydrogenase deficiency. In addition, vitamin E shifts the intracellular redox potential enough to ameliorate the oxidative environment caused by a deficiency of reduced glutathione which is caused by a deficiency of NADPH. Other investigators have also reversed the susceptibility of red and white blood cells to oxidative damage in patients with glutathione synthase deficiency with large doses of vitamin E.

Research of genetic-nutrient interactions in animal models aims to establish possible interactions of mutant and inbred animal models with trace elements; to elucidate their mechanism of action; and to investigate the interaction of nutrients, genes and drugs. Manganese deficiency has been shown to depress the activity of superoxide dismutase (SOD), the enzyme which catalyzes the dismutation of superoxide free radicals and acts as an inhibitor in both reducing and oxidizing reactions. In one study, the activity of MN-SOD in the liver of manganese deficient mice was 17 percent that of controls, while activity in the brain was reduced by 50 percent. This decrease in MN-SOD activity causes an accumulation of free O_2 inside the mitochondria and may thereby explain the membrane damage, particularly in the mitochondria, caused by the manganese deficiency.

Investigators have delineated the effect of the mutant gene "crinkled" in mice on copper metabolism, and the relationship between dietary copper and the effects of the mutant gene "quaking." Liver CuZnSOD activity was lower in crinkled mice than in littermate controls at 14 and 60 days of age, while liver copper concentration was also low at 14 days but normal at 60 days. Data indicate that a high level of dietary copper supplementation during pregnancy and lactation increases CuZnSOD activity and copper concentration in the liver of mutant offspring to levels similar to those of littermate controls. Studies on the effect of copper supplementation on the "quaking" mutant (qk) mouse indicate that the postnatal period is the critical period for copper supplementation. This observation is consistent with the finding that the qk gene does not manifest itself until 10 days postpartum. Thus, copper supplementation during the prenatal period appears to have no beneficial result on the frequency of tremors, although it does help to treat the manifestations of Menkes kinky hair syndrome.

Analysis of the influence of combined genetic and nutritional factors on drug teratogenicity continues to improve our understanding of the interactions between genetic and nutritional factors in mammalian development. For example, high levels of dietary zinc may ameliorate the deleterious effects of 6-mercaptopurine on embryonic DNA metabolism and maternal toxicity. In addition, increasing levels of dietary zinc in the CBA mouse was found to reduce acetazolamide induced fetal malformations. This teratogen inhibits carbonic anhydrase by binding to the zinc ion at the enzyme's active site. The interaction between zinc and acetazolamide appears to be influenced by genetic background.

Research on the nonnutrient components of food, i.e., the intentional additives and the accidental chemical contaminants, explores the various facets of adverse biological effects associated with long-term low level exposure. Metabolic functions, interactions with cellular macromolecules, and mechanisms of toxic action are examined in order to assess mutagenicity and carcinogenicity risks of toxic substances in food. Investigations continue on the genetic regulation of aflatoxin metabolism, and the characterization of its precursors, pathogenesis, and mechanisms of carcinogenesis and toxicity. The common flavonols, quercetin and kaempferol, are being tested for mutagenicity in Salmonella typhimurium in order to determine the carcinogenic insult to intestinal epithelium.

Other studies on carcinogenesis, genetics and nutrition include: investigations on the specificity of amino acid effects on albumin synthesis and of the regulation of amino acid synthesis *in vitro* under both metabolic and genetic control of hydroxylation rates; examination of the relationship of structural modifications of cell membranes with the cocarcinogenic action of cyclopropanoid fatty acids in diets with mycotoxins; and attempts to identify markers (e.g., restriction fragment length polymorphisms, sister chromatid exchange rates, and polyamine levels in breast fluid) specific for a cancer prone genotype in order to identify individuals at risk for cancer. One study of female breast cancer within disease-discordant twins evaluates demographic, environmental and medical histories of the twins and their families from registries in Denmark, Finland, Norway and Sweden. Familial clusters of cancer in the Mormon population are also being studied.

Additional studies of nutrition-related genetic disorders include research on hereditary diabetes, genetic factors in obesity and diabetes, genetic and hypothalamic obesity, the effects of dietary restriction in obese (FA/FA) rats, pancreatic polypeptide in the control of body weight, the physiological basis of polygenic obesity in mice, the role of beta endorphin in obesity, the pathogenesis of human cystinosis, and Cooley's anemia and iron storage disease, familial lipid patterns and coronary heart disease.

The San Antonio Heart Study is an epidemiological study assessing "diabetic pattern risk factors" (obesity, glucose intolerance, hypertriglyceridemia, and low levels of high density lipoproteins) in Mexican Americans. It is believed that as Mexican Americans acculturate to U.S. lifestyles that they will gradually lose their excess of risk factors.

Other studies of coronary heart disease, atherosclerosis, and familial lipid patterns are also under way. Investigators have found a decrease in the activity of cholesterol ester hydrolase (CEH) in the mononuclear cells of patients with symptomatic atherosclerosis, as well as in hyperlipidemic and diabetic individuals. The basic hypothesis being tested is that blood monocyte CEH activity may be predictive of intimal smooth muscle cell CEH activity. Therefore, decreased CEH activity increases the risk for progressive atherosclerosis due to the impaired cholesterol ester hydrolytic activity in the arterial smooth muscle cell. Patients with familial hypercholesterolemia, diabetes mellitus, and those who have had strokes or transient ischemic attacks are being

studied. Another study is investigating the premise that metabolically active tissues can undergo a progression or regression of atherosclerotic plaques. Parameters being measured in patients on a low cholesterol diet and a typical U.S. diet include cholesterol turnover rate of both the free and cholesterol ester pools, the rate of cholesterol esterification, and the rate of cholesterol ester glycolysis in the arterial wall.

Epidemiological Research in Nutrition

Epidemiological research in nutrition examines the role of food habits and the socioeconomic factors that influence food selection in health and disease conditions. As a result, important relationships between diet and cancer, and between diet and cardiovascular disease have been revealed. Improved methods for assessing food intake and factors that influence food selection also have been developed. In FY 1982, support from NHLBI, NCI, NICHD, NIADDK, NIDR, NIA, NIAID, DRR, NIEHS, and NEI for projects with significant epidemiological nutrition research components amounted to \$18,912,000 or 13 percent of total nutrition research.

The five basic categories of studies in this area include: 1) studies to evaluate methods and procedures used in epidemiological research in nutrition; 2) studies of nutrition's role on the physical and psychological development in defined populations; 3) nutrition-related epidemiological studies on maturation and reproductive functions; 4) surveys of nutrient intake and nutritional status assessment of special population groups; and 5) studies on the correlations of food intake to disease states.

Research on the effect of early nutrition on physical and psychological development, and maturation and reproductive function includes studies on correlates of adipose cell growth in infancy; the determinants of changes in fatness with age; the effect of environmental factors on childhood obesity; the effect of home-based behavioral programs on the treatment of obesity; the clinical correlates of vitamin D status in infants; the association of zinc deficiency with failure to thrive in infants; and the effect of diet and oral hygiene on caries development in school age children living in a fluoride free community. Studies of pregnant and lactating women examine the effect of folate deficiency on neural tube defects in the infant, the trends in breast and bottle feeding among groups of women in the U.S. and other groups such as the Pima Indians and the Negev Bedouins, and the effect of diet, alcohol and smoking on lactation and subsequent infant growth.

The antecedents and effects of breast and bottle feeding on infant growth and development are being analyzed also from data collected on 19,044 babies born to women pregnant between August 1959 to September 1966. Data collected on the mothers include socioeconomic status, educational level attained, smoking and drinking habits, drug and coffee intake, and obstetrical history.

An epidemiological study on the influence of diet to the age of menarche revealed no differences between a group of girls on strict vegetarian diets and those on a typical American diet.

Epidemiological studies on diabetes mellitus have been carried out in the Gila River Indians, Oklahoma Indians, and the Pima Indians. The longitudinal study of the Pima Indians examined the relationship between obesity in children and diabetes during pregnancy in their mothers. The study revealed that within each age group, the offspring of the diabetic women had much higher rates of obesity than the offspring of either nondiabetic or prediabetic women. This effect was seen regardless of maternal body-mass index and was observed throughout the period of observation. For example, at 15 to 19 years of age, 58 percent of the offspring of diabetics weighed 140 percent or more of their desirable weight as compared with 17 percent of the offspring of nondiabetics and 25 percent of those of prediabetics.

This study suggests that the excessive severity and frequency of obesity in the offspring of diabetic mothers is due largely to the abnormal intrauterine environment and fetal overnutrition. The strong relation between the third trimester plasma glucose concentration and birth weight in the Pima population support the concept that the third trimester is an important period of intrauterine overnutrition. Thus, maternal diabetes during gestation may be one cause of obesity that may subsequently lead to diabetes in offspring. Controlling diabetes during pregnancy could be a first step in obesity and diabetes prevention in offspring.

An important component of the research carried out in this area includes cross-cultural surveys and case control studies that evaluate the relationship between nutrition and cancer etiology. Dietary exposures being assessed in human populations include consumption of specific food items and food groups (such as coffee, ethnic dishes, meats, fruits and vegetables) and macronutrient and micronutrient intake (such as fat, vitamin A, carotene, vitamin C, or folacin). These studies also investigate general nutritional status; anthropometry; biochemical indices such as serum cholesterol, serum vitamin A, or serum uric acid; and cooking practices. Cancers being studied include those of the colon, rectum, breast, esophagus, pharynx, oral cavity, lung, cervix, pancreas, stomach and kidney.

Studies are being carried out in targeted areas with unusually high mortality rates from cancers. For example, a case control study of esophageal cancer in black male residents of Washington, D.C. (the U.S. metropolitan area with the highest rate of esophageal cancer among black males) has shown that the consumption of meat and fish, dairy products and eggs, fruits and vegetables; the number of meals consumed each day; and relative weight (wt/ht) were each significantly and inversely correlated with the relative risk of esophageal cancer. None of the associations were markedly reduced by controlling for ethanol consumption, smoking, socioeconomic status, or other nutrition measures. Poor nutrition, in general, appeared to be the major dietary predictor of risk to esophageal cancer in this population.

A breast cancer study conducted in Alberta, Canada, where breast cancer rates are the highest in the world, suggests a significant increase in risk with the more frequent consumption of beef, pork, and sweet desserts. The study of oral and pharyngeal cancer among North Carolina women appears

to suggest a protective effect of a diet high in fruits and vegetables. Additional case control cancer studies with a nutrition component include: lung cancer in New Jersey and in the Gulf Coast area of Texas; lung, pancreas, and stomach cancers in Louisiana; breast cancer in Israel; esophageal cancer in Charleston, Savannah and Jacksonville, Florida; urothelial cancer and prostate cancer in Hawaii; bladder cancer in Utah; leukemia and thyroid disease in Utah; and esophageal cancer in Iran.

In addition, studies are under way in special populations such as migrant workers whose changing cancer rates appear related to new lifestyles. Studies of migrant populations include three case control studies of colorectal cancer, one in persons of Czechoslovakian ancestry living in rural Nebraska, one in Mormons living in California, and the other of persons from the Northeast and North Central states living in three regions of Florida.

From the Nebraska study, the excess risk of colorectal cancer was primarily among persons with Czechoslovakian ancestry, particularly those from Bohemia and Moravia. The elevated risk among Bohemians was associated with diets high in fat and sweets and consumption of commercial beer, while the elevated risk among Moravians was associated with intestinal polyps and a familial history of gastrointestinal and other cancers.

Examination of the age-specific cancer mortality rates in three regions of Florida with high rates of immigration from the Northeast and North Central states has revealed that in these counties the colorectal cancer rates were as low as in southern counties of comparable populations and did not rise toward the northern rates at the older retirement age. This study will attempt to determine whether this reduction in risk is due to some change in lifestyle (e.g., diet or drinking water) or to the migrants being a self-selected healthy subset of northerners.

A prospective study of 120,000 women includes the collection of data on dietary intake practices, contraceptive practices, cigarette smoking, hair dye use, and pertinent demographic and gynecological histories. These data will allow the assessment of potential causal associations between breast cancer incidence and diet (i.e., intake of total fat, linoleic acid, trans fatty acids, saturated fat, cholesterol and caffeine); the determination of possible protective associations of retinol, carotene, vitamins C and E, and fiber; investigation of potential causal associations between fat intake, use of processed foods and the incidence of colon cancer; determination of potential protective associations between cruciferous vegetables, fiber, carotene and retinol, and vitamin C and colon cancer; and the evaluation of a potential protective association in smokers between the intake of retinol, carotene, vitamins C and E, cruciferous vegetables and the development of lung cancer. The protective or possibly causal associations of various dietary factors, artificial sweeteners, and alcohol use and the incidence of ovarian, uterine, bladder and skin cancer are also being considered.

Other prospective studies investigate heavy analgesic consumption, occupational exposures, cigarette smoking and coffee consumption in cancer of the renal pelvis and ureter.

One study of 21,900 male physicians between the ages of 50 to 75 years is under way to assess the chemopreventive effect of alternate day consumption of 30 milligrams (mg) of beta-carotene, as well as the effect on cardiovascular mortality of alternate day consumption of 325 mg of aspirin. Participants are randomized into one of four treatment groups: one 325 mg aspirin tablet every other day alternating with one 30 mg capsule of beta-carotene; one aspirin every other day alternating with one capsule of beta-carotene placebo; one aspirin placebo tablet every other day alternating with one capsule of beta-carotene; and one aspirin placebo tablet every other day alternating with one capsule of beta-carotene placebo. The incidence of cancer in this population will be assessed as well as cardiovascular mortality, coronary events, and total mortality.

A case control study under way in North Carolina evaluates the relationship of colon cancer and drinking water quality. Water quality indices for the past 20 and 30 years are being developed based on water source, treatment and prior use characteristics, and will provide some insight on the importance of water borne carcinogens in the etiology of a known cancer site. Estimates of cancer risks at various exposure levels will be obtained.

Additional large-scale studies investigate dietary factors associated with coronary and vascular diseases. The Lipid Research Clinics (LRC) Program-Coronary Primary Prevention Trial that includes 3,810 subjects will come to a close after more than 7 years in August 1983. The data from the LRC Prevalence Study on lipid/lipoprotein distributions in 10 North American cities compare the prevalence of high lipid and lipoprotein levels in various age, race, ethnic and social groups. The Framingham Heart Study also investigated the role of diet on lipid and lipoprotein levels. The data indicate that in younger adults (20 to 50 years) alcohol consumption was highly associated with high density lipoprotein levels (HDL), while obesity and cigarette smoking were associated with all lipid fractions. Thus, in persons under 50 years of age, environmental factors are indeed associated with lipoprotein cholesterol profiles.

In terms of coronary heart disease morbidity and mortality, a number of investigators are studying the effect of alcohol consumption. A prospective study of 10,000 Yugoslavian men found a significant inverse relationship of alcohol consumption to coronary heart disease incidence even after accounting for differences in blood pressure, serum cholesterol levels, cigarette smoking and other variables. Since the protective effect of alcohol was absent for sudden death, it may reflect the deleterious effects of high alcohol consumption on the myocardial cells and increased vulnerability to lethal arrhythmias in an especially lean population.

In addition, of the 9,150 men who participated in the Puerto Rico Heart Health program, those who were moderate drinkers appeared to have the lowest incidence rates for nonsudden coronary death. The older and poorer members of this population, however, did not share in this benefit. Thus, it is premature to recommend moderate drinking as protection against coronary artery disease. Studies continue to examine the relative risk of myocardial infarction of moderate alcohol consumers and nondrinkers when HDL and other established risk factors are controlled.

Other studies examine the coronary risk factors in school age children in terms of familial dietary patterns and incidence of coronary disease, and the epidemiology of blood pressure. For example, 175 white children and 115 black children are being examined at ages 3, 4, and 5 years for blood pressure, heart rate, weight and height. This study will assess the age in different ethnic, socioeconomic, and sex groups that: 1) tracking of blood pressure and heart rate persists; 2) weight and change in weight is associated with blood pressure levels; and 3) whether the level and distribution of blood pressure levels in families with infants having elevated blood pressure differs from families with infants having low blood pressure. Tracking of blood pressure has been demonstrated in children; i.e., children with high blood pressure continue to have high blood pressure over time. Multivariate analysis to examine predictors of tracking blood pressure will be made and thus help define appropriate strategies for primary prevention of hypertension.

The study of biological and sociocultural variables associated with blood pressure levels of 8,000 Japanese men living in Hawaii has been completed. From an analysis of more than 50 variables, it appears that obesity, age, hematocrit, heart rate, forced vital capacity, serum triglycerides, serum uric acid, cigarette smoking, and family history of hypertension are all independently associated with both cross-sectional levels and longitudinal changes in blood pressure. Among this cohort, milk intake was inversely associated with both systolic and diastolic blood pressure.

Nutritional Status

Research on nutritional status includes investigations to develop and evaluate various kinds of methods useful to determining the requirements of essential nutrients throughout the life cycle from fetal life to infancy, childhood, adolescence, adulthood, and the aged. Studies carried out in both normal and patient populations examine biochemical, anthropometric, maturational, and functional indices of nutritional status; methods to measure nutrient concentrations in various tissues and plasma; and dietary recall methods. The NIH is the major agency that supports research for the development of methods used in nutrition surveys. In FY 1982, research on nutritional status was supported by NICHD, NHLBI, NIADDK, NCI, DRR, NIGMS, NIDR, NIAID, and NEI in the amount of \$17,827,000 or 12 percent of total nutrition research.

Reliable methods for assessment of nutritional status are needed in order to: 1) determine whether or not impairment of health is the result of inadequate or inappropriate diet; 2) establish the specific nature of any nutritional problem underlying such health impairment; 3) provide knowledge on which to base dietary treatments for improving health; and 4) permit evaluation of the effectiveness of nutritional treatments or interventions that may be undertaken to improve health.

Methods to assess nutritional status include anthropometric measurements of weight and height, and skinfold thicknesses; biochemical measurements including assays for serum and tissue levels of various vitamins, minerals, fatty acids and amino acids; balance studies to assess bioavailability, absorption and metabolic status of trace elements, etc. Some

of the specific methods being tested in the newborn include a prototype volume measuring instrument that consists of two chambers, a reference chamber and a measuring chamber that contains the infant. Infants fed various diets are placed in the chamber and the volume of each chamber is decreased cyclically; the pressure difference between the reference and the measuring chamber is determined with a differential manometer. Once perfected, this instrument will provide the first truly non-invasive means of assessing body volume changes in growing infants. Another noninvasive method for the evaluation of lean and fat mass in normal and premature newborn infants consists of an instrument that sets up an electromagnetic field which becomes perturbed by the introduction of electrolytes into the field. The degree of perturbation in the field is a function of the amount of electrolytes that reside almost exclusively in the lean body compartment.

Noninvasive techniques are also being used to provide additional insight on the metabolism and absorption of specific nutrients in the newborn; for example, a number of carbohydrates (glucosamine, galactosamine, galactose, fucose, and sialic acid) are being analyzed for their contribution to the pulmonary excretion of gaseous hydrogen, ^{13}C labeled carbon dioxide and methane. This method is being used primarily to assess the status of the digestive and absorptive properties of premature infants, as well as infants with cystic fibrosis.

The bioavailability, absorption and metabolic status of calcium, iron, and zinc provided to premature infants in specialized formulas are being assessed through stable isotopes used in balance studies. Another component of this study includes examination of the transfer of these specific elements from lactating mothers to their infants. These studies help to assess the precise needs of the premature infant for trace metals in the diet, the best form in which to supply them, and the effect of the trace metal status of the lactating mother on the transfer of nutrients to the infant.

Zinc deficiency is a prevalent nutritional problem worldwide due to a high consumption of grains and cereals with phytate that bind zinc, as well as a number of diseases and disorders such as cirrhosis of the liver, sickle cell disease, prolonged hyperalimentation, and in states of malnutrition, etc. Since zinc deficiency appears to have a destructive effect on the immune system, a number of studies are under way to examine the interrelationship of zinc to the integrity of the immune system. Data from animal studies have shown that diets deficient only in zinc ($0.6 \mu\text{gZn/g}$) severely impaired delayed type hypersensitivity (DTH) to dinitrofluorobenzene (DNFB). Zinc replacement permitted normal DTH responses within 3 weeks. Examinations of whether the immune dysfunction is due to a uniform decrease in the number of lymphocytes or to selective decreases in certain subpopulations of these cells have revealed that: A) the T-cells vary in their sensitivity to zinc deficiency, and B) splenocytes show depressed responses to concanavalin A (50 percent), equivalent responses to phytohemagglutinin, and elevated responses in the mixed lymphocyte culture (100 percent) compared to control splenocytes. A marginal zinc deficiency in mice has also been shown to arrest growth and the development of their immune systems; responses to T-cell dependent

(SRBC) and T-cell independent (dextran) antigens were reduced significantly in the deficient neonate.

The effects of zinc deficiency on skeletal and dental tissue has been recognized, especially in rats subjected to protein calorie malnutrition. The deficiency state is reversed when picolinic acid supplements at 0.2 gm/kg of diet are provided to the animals. Picolinic acid appears to aid the transport of zinc through the intestinal wall.

In addition, children with diabetes mellitus who also exhibit growth retardation and delayed sexual maturation may have excessive losses of zinc. Studies are under way to determine the zinc status of these children and to evaluate the effect of zinc supplements.

Another possible method to assess the zinc status in man is by monitoring the activity of RNAase, a zinc dependent enzyme. In a study of young adult men fed a zinc deficient diet for 8 weeks, this enzyme's activity was increased significantly in the plasma and parotid saliva and returned to normal with zinc repletion. The zinc depleted men also exhibited leukopenia with relative lymphocytosis. In persons with impaired dark adaptation or night vision, zinc supplements were found to correct the impairment in adults not responsive to vitamin A. Tests used to assess dark adaptation as a functional measurement of vitamin A may therefore also be used to identify zinc deficiency.

Since early detection of hypovitaminosis A and the institution of prophylactic therapy can dramatically reduce the prevalence of xerophthalmia and vitamin A deficiency, a rapid dark adaptation test for use in the field is extremely important. A test which matches the color intensities of various discs to cone function rather than rod function has been developed and used with 95 percent sensitivity and 91 percent specificity. The test is based on the shift of retinal wavelength sensitivity as the eye dark adapts, and the need for the subject to separate sequentially the white and blue discs from a pile of red, white and blue discs. This test has been used satisfactorily with children aged 4 to 13 years under field conditions in Guatemala and in Baltimore.

Assessment of blood and urinary levels of vitamin A or its metabolites do not reflect tissue reserve stores until they become very depleted. A new method being tested to assess marginal states of vitamin A deficiency involves an oral challenge of small amounts of vitamin A and measurements of blood levels pre and 5 hours post dosing (the relative dose response, RDR). Such a method will allow persons in the field to identify for the first time marginal states of vitamin A deficiency.

A new method to study both the nutritional aspects of iron absorption and the movement of iron through the plasma has been developed. The "small dose iron tolerance test" involves the oral administration of 5 to 30 mg. of iron as sulfate or fumarate and the measurement of plasma iron concentrations at intervals for 8 hours. Persons mildly iron deficient exhibited significant increases in plasma iron concentrations during the first several hours, while the iron replete individuals had no changes in plasma iron. The iron tolerance curves vary with differences in total body iron status.

Assessment of nutritional status of obese and anorectic patients involve measurements of body composition and energy expenditure. One study of weight reduction in obese adolescents has revealed that a liquid protein diet of 500 calories per day, provided over a 34 to 48 day period, precipitated approximately 50 percent of the weight loss due to a loss in lean body mass. When this regimen is extended for an additional 4 months, the loss in lean body mass is reduced to 8 percent of total weight loss. It is interesting to note that with deliberate overfeeding for 3 weeks, approximately 40 percent of the weight gain consists of lean tissue gain. Thus, obese individuals appear to have significantly greater lean body mass than comparable nonobese subjects of similar stature.

Studies are under way to validate the double labeled water method for measuring energy expenditure; water made from the stable isotopes of ^2H and ^{18}O is administered and the ^2H lost in $^2\text{H}_2\text{O}$ and ^{18}O lost in $^{18}\text{CO}_2$ is measured. This method will be compared with indirect calorimetry as a reference.

The use of nonradioactive stable isotopes have recently appeared to offer significant advantages over radioactive methods to assess nutritional status, especially of pregnant women and infants and children. Only small quantities of foodstuffs labeled with the stable isotopes of hydrogen, carbon, nitrogen, and oxygen are ingested, thereby making the procedure both noninvasive and cost effective. The technique also allows for interval measurements of enzyme activity.

A breath analysis test using the stable isotope technique to analyze carbon dioxide in the breath has been shown to be useful for measuring the rates of fat and carbohydrate absorption and metabolism. This test has been used to investigate the ability of a 1-month-old infant to utilize starch or corn syrup polymers when they replaced sucrose in the infant formula. Since the corn products are naturally enriched with the isotope of carbon used in the test, the appearance of labeled carbon dioxide in the breath demonstrated for the first time that a caloric benefit to the infant resulted from the ingestion of these complex carbohydrates. Analyses of fecal contents for the isotope confirmed that the starch was largely (more than 85 percent) absorbed. At least a portion of the starch is eventually scavenged from the colon as volatile fatty acid. This breath analysis test can be used to study normal premature infants, as well as infants with metabolic acidosis, acute diarrhea, and other problems.

Many studies also investigate the relationship of food intake, nutritional status, and functional performance especially in terms of reproduction, work performance and cognitive development. For example, the effect of marginal zinc or copper deficiency on spermatogenesis is being examined with atomic absorption techniques to establish the location of copper, manganese, zinc, and selenium within sperm cells. Zinc appears to be incorporated into sperm keratin that imparts structural integrity to sperm cells. Studies on the relationship of nutritional status to cognitive performance have broad implications in terms of school performance in undernourished children both in this country and abroad.

Maintaining an appropriate nutritional state is often difficult in the cancer patient whose metabolic processes bear the brunt of tumor insult, chemotherapeutic measures, and resultant anorexia. A study of cancer patients whose basal metabolic rates were evaluated by indirect calorimetry revealed that compared to controls, cancer patients were hypermetabolic. The basal metabolic rates, normal for surface area, were elevated for lean body mass. In addition, the malnourished cancer patients appeared to be deficient in anabolic hormones (growth hormone and testosterone), to have inappropriately elevated triiodothyronine levels, and to have excessive amounts of anti-insulin hormones.

Nutritional assessment methods for measuring adipose, musculoskeletal, cardiac, and visceral components of cancer patients with protein calorie malnutrition are being developed. Since measures of whole body counting using prompt gamma neutron activation (^{40}K and ^{14}N) provide clinicians with an understanding of the effect of diet on muscle mass and other lean body compartments, studies are currently being carried out to look at the effect in cancer patients. The accuracy of computerized tomography (CT) scans in measuring limb, fat, muscle and bone volume has been standardized and evaluated in both normal and cancer patients. It appears that because the CT scan offers a rapid, reproducible, accurate, and non-invasive method of measuring the mass of internal organs and body composition that it has become an important technique for the evaluation and subsequent management of patients with malignancies.

A multi-institutional cancer study is under way to assess the efficacy of two levels of nutritional support in maintaining lean body mass by providing a constant energy supply. A number of investigations attempt to detect correlations and significance of clinical and laboratory estimates of nutritional status in order to gain a better understanding of the clinical relevancy of particular parameters. One investigator is performing kinetic studies on patients with gastrointestinal cancer in order to quantitatively evaluate energy expenditure and the composition of the diet mixture being burned. This research will provide information related to the amount and kind of nutritional support appropriate for cancer patients.

The appropriateness of various total parenteral and enteral nutrition solutions are being tested in patients with various malignancies; the nutritional status of these patients is compared to a normal population through the use of many nutritional assessment parameters. The long-range effects of nutritional support are being assessed by tolerance to chemotherapy, performance status, tumor response, and survival. In one study of nutritional support in metastatic colorectal patients, hyperalimentation increased the rate of lactate production with a significant increase in carbon dioxide production. This study also revealed that increased basal lactate production and impaired glucose tolerance existed, independently of each other.

Research on the assessment of nutritional status in the patient population is also a priority of the Clinical Nutrition Research Units.

Investigations on the nutritional status of populations attempt: to determine whether specific health impairments, attributable to inadequate or inappropriate diet can be identified in a significant proportion of the population; to establish the nature of the dietary problem responsible for any such impairment; to provide information as to whether some action should or can be undertaken to remedy any present or foreseeable health impairment; and to evaluate any intervention that may be undertaken. A major research challenge is to improve the ability to differentiate between associations that are coincidental and those that are biologically significant as predictors of the health impairment under study.

A number of studies concerned with evaluating the effectiveness of dietary interventions on nutritional status and the risk for cardiovascular disease and hypertension are currently under way. For example, one of the intervention groups of the Hypertension Prevention Trial employs dietary restrictions, i.e., salt, in an attempt to control hypertension. This trial also examines the correction of overweight as a treatment of hypertension. Another cohort of 8,000 Japanese men living in Hawaii was examined for factors associated with high blood pressure. Those factors shown to be independently associated with both cross-sectional levels and longitudinal changes in blood pressure were obesity, age, hematocrit, heart rate, serum triglyceride, serum uric acid levels, cigarette consumption and family history of hypertension. Other studies are examining the relationship of alcohol consumption to the incidence of coronary heart disease, morbidity and mortality.

In epidemiological studies and surveys of populations, nutritional status assessment measures include methods to screen individuals as well as to assess and monitor populations. When either an intervention program or survey is undertaken, standardized data collection and adequate data handling facilities ensure quality information that is available rapidly for analysis and utilization. Well documented data sets made available to agencies and scientists involved in studies of nutritional epidemiology will facilitate improvements in such studies.

An intervention project to assess dietary intake and nutritional status also requires data on food composition that accurately reflect the nutrients found in the food supply. Determining the reliability of food composition data is an ongoing process. Research must continue to be directed towards the development of improved methods of obtaining and analyzing food consumption data. Data on food consumption must also be integrated with information on health status, demographic characteristics, behavioral and particularly attitudinal measures.

Nutrition and Obesity

Obesity is a major health problem in the U.S., affecting both children and adults. Data from the NHANES I survey show that overweight affects a significant proportion of our population; 14 percent of the men and 24 percent of the women between ages of 20 to 74 years were found to be 20 percent or more above their desirable weight. One of every three women past the age of 55 is overweight. Similarly, data from the second NHANES (1976 to 1980) indicate that the prevalence of obesity persists and that

those in the 90th percentile are even heavier than in previous surveys. Obesity is associated with hypertension, hyperlipidemia and hypercholesterolemia, diabetes, and osteoarthritis, and contributes to increased postsurgical infections and complications of pregnancy. It has recently been shown to be an independent risk factor for cardiovascular disease. Consequently, research on the biomedical and behavioral aspects of obesity is an important area of consideration at the NIH. In FY 1982, a total of \$17,118,000, or 12 percent of total NIH nutrition research, was spent on studies of the etiology, treatment, and prevention of this condition. DRR, NIADDK, NICHD, NHLBI, NCI, NIA, NINCDS, and NIGMS supported research in this important area.

Research is under way to examine the genetic, metabolic, clinical, environmental and behavioral aspects of obesity in humans and in animal models; to define the types of obesity; and to establish better methods of prevention and treatment. Studies of the developmental aspects of obesity, its natural history, and its heterogeneous origins attempt to identify determinants of obesity in infancy, childhood and adolescence.

Research on the natural history and development of obesity has shown that obesity during infancy does not predict obesity at 12 years of age, whereas obesity at 2 to 3 years for girls and 3 to 4 years for boys is a good predictor for adolescent obesity. No significant differences due to breast or bottle feeding were found in the obese and nonobese 12-year-old children, suggesting that obesity at 12 years of age may not be related to the type of infant feeding.

A longitudinal study of fat cell growth in infants has reported that fat cell size increases during the first 6 months of life and decreases from 7 through 55 months. Fat cell number, however, increases from birth through 55 months. In addition, infants fed at longer intervals had greater weight for height ratios than infants fed on demand. An inverse relationship between age at introduction of solid foods and infant weight for height ratios was also reported. Another investigator is examining the relationship between infant suckling behavior and growth indices in infants, as well as the relationship between physical activity levels and growth indices in young children between the ages of 4 and 8 years whose neonatal physical activity had been previously obtained.

Results of a large consortium grant assessing the natural history of obesity in 2,500 individuals between the ages of adolescence through the fifth decade indicate that fat cell number, total body fat and percent body fat increase in both men and women with increasing age. Women, however, have significantly more body fat and larger fat cells in their third decade, while men have more total body fat than women in the fifth decade. Of particular interest are the data indicating that obesity during infancy does not predict adult obesity, while obesity after four years of age does predict obesity in adulthood thus confirming the finding of a previous study described earlier in the report. Adolescent boys in the study appeared to have a near zero mean increment in total body fat, whereas girls had a positive increment with age. Total body fat in boys did not change significantly, whereas girls did experience a mean annual increase. Continuity between adolescent fatness and adulthood obesity

appeared strong. In addition, familial correlations for obesity at the same chronological age are more similar for the first generation than for the second or third generations. Triceps skinfold measurements appeared as the best single indicator of percent body fat, and the ratio of body weight for height² (Body Mass Index - BMI) the best single indicator of total body fat.

Data on obesity from the Ten State Nutrition Survey and Tecumseh Study indicate that obesity falls along socioeconomic gradients and is most common in lower income females and median income males in both the black and white populations. The black female is generally fatter than the white female, however, at comparable levels of education, income or occupation both blacks and whites have comparable levels of fatness. Obesity also appears to follow family lines; that is, a child of two obese parents has greater than a 300 percent chance of becoming obese and at adulthood is likely to become over 300 percent fatter than a comparable child of lean parents. One fat sibling is likely to have another fat sibling about 40 percent of the time. The genetic hypothesis to obesity, however, appears challenged by husband and wife similarities in fatness, as well as by similarities between adopted children and their parents. Fatness seems to be familial but not necessarily genetic; continuity of fatness levels appears to be as much a social or cohabitational effect as a biological effect.

Basic research on the pathogenesis of obesity includes studies on adipose cell morphology, thermogenesis, hypothalamic function, hormonal regulation, satiety signals, suitable methods for measuring body composition, and psychological factors underlying eating behaviors. Studies continue to examine fat cell size and fat cell number. Recent observations confirm the finding that extreme food deprivation does not alter fat cell number in the rat; i.e., adipocyte turnover was not evident following starvation using the radioactive labeled DNA precursor ³H-thymidine.

Investigations of the genetically obese (FA/FA) Zucker rat have shown that with lateral hypothalamic lesions, the adipose cell number and size can be reduced to that of lean litter mates. When fed a diet that increased carcass lipids, neither the lesioned rat or the lean control showed any increase in fat cell number. In addition, the lean control rats maintained a higher body weight than pair-fed lesioned rats. The lesioned FA/FA rat, as well as the obese FA/FA rat, had elevated plasma insulin levels and reduced protein deposition with food restriction. It seems possible that lateral hypothalamic lesions affect a mechanism that sets the level of adiposity and possibly adipocyte number.

The working hypothesis of obesity which holds that hypothalamic pituitary dysfunction and altered neuroendocrine secretions cause decreased thermogenesis and/or increased food intake is under investigation. Changes in thyroid and catecholamine metabolism are being investigated. In studies of rats with ventromedial (VMH) hypothalamic lesions, the resting metabolic rate appeared to be 10 to 18 percent less than nonlesioned controls of similar body weight. Thus, the reduced basal energy expenditure in VMH lesioned rats suggests that the obesity caused by this lesion is due to

an alteration in energy expenditure. Another study of VMH lesioned weanling rats examined norepinephrine turnover rates in various tissues as an indicator of sympathetic nervous system activity in relation to obesity. These rats had 38 percent less norepinephrine turnover in brown adipose tissue.

Brown adipose tissue (BAT) may have a very important role in the overall expression of the thermic effect of single meals in rats. The respiration rate of BAT differs with the nutrient content of the meal; i.e., the rate following a high carbohydrate meal is greater than after a high fat meal. Significant changes in the metabolic activity, amount and composition of BAT are apparent in response to single meals, therefore BAT and thermoreceptors in BAT may be linked to food intake control mechanisms. In studies of rats given diets of either sucrose, glucose, or fructose, and a standard diet, the rats given sucrose had the most BAT. Rats on any of the sugar diets had significantly more BAT than controls. Brown adipose tissue also appears to be important for the body's adaptation to the cold, and for metabolizing fuel to free energy when excess energy is consumed.

A number of factors known to control satiety are also being investigated. The satiety effect of bombesin (BBS) and cholecystokinin (CCK) appear to be due to different mechanisms; e.g., abdominal vagotomy in rats abolished the satiety effect of cholecystokinin, but not that of intraperitoneal BBS. In baboons, small doses of BBS (1 ug/kg) reduced food consumption, slightly increased basal immunoreactive insulin (IRI), and suppressed postprandial increases of IRI. Additional studies of satiety in humans have shown that intravenous infusions of cholecystokinin-8 given to obese and lean men decreased food intake by 12 to 13 percent in both. Thus, obese men are as sensitive to the satiety effect of CCK-8 as lean men.

Research results also suggest that gastric distension per se is a potent satiety signal. In studies with rhesus monkeys, glucose intake was significantly reduced in those monkeys who after a 15-minute drinking bout had their stomach contents removed and refilled with non-nutrient saline, as compared to monkeys whose stomachs remained empty. Gastrin releasing hormone (GRH) also has been shown to elicit in rats the complete behavioral sequence of satiety and a dose-related suppression of meal size. Additional studies of rats given microinfusions of 5 thioglucose into the lateral or fourth ventricle of the brain suggest that the glucoreceptors that mediate feeding behavior and hyperglycemia in response to glucoprivation are located in the caudal hindbrain and not in the hypothalamus. Research is continuing in this area.

The influence of physiological regulators versus psychological drives on food intake is under investigation. The physiological control of food intake appears to override any psychological drive to consume highly palatable foods. This physiological control responds to changes in the palatability, caloric concentration, quantity of the food, etc. eaten on an average day. Increases in plasma glycerol levels, or glycerol in relation to free fatty acids, however, do not appear to reduce voluntary food intake in man.

Several metabolic and/or neural mechanisms may be involved in the maintenance of body weight and the maintenance of homeostasis with respect to specific metabolites. Overeating that leads to obesity could result from adaptive dietary responses to environmental "stress" within genetic capabilities. One hypothesis being tested is whether nutrient imbalances, toxicities or metabolic deficiencies turn off physiological appetite, while suboptimal but adequate levels stimulate the drive to overconsume energy. Studies on other possible causes of obesity have revealed that canine distemper virus and herpes simplex virus induced obesity when injected into young adult mice.

Due to the serious health implications of obesity, much of the research in this area attempts to uncover successful treatment measures that prevent its recurrence. In one study, individuals given 800 calorie diets differing in carbohydrate and fat lost similar amounts of lean and fat tissue with weight reduction. In addition, urinary calcium excretion was increased--presumably due to acidemia, which accompanies low calorie ketogenic regimens--thereby indicating the need to include sufficient carbohydrate in any hypocaloric regimen in order to prevent osteopenia. Studies on "protein-sparing" low calorie diets indicate that hypocaloric diets consisting only of protein do not spare more body nitrogen than an equivalent mixture of protein and carbohydrates. In addition, low calorie diets consisting of protein and carbohydrate appear to maintain nitrogen balance and spare lean body mass much better than do isocaloric diets of protein and fat.

Studies in obese subjects made ketotic by starvation examine the effect of carbohydrate intake on the modulation of leucine oxidation and turnover. Results suggest that ketosis directly or indirectly enhances leucine oxidation; carbohydrate diets providing 300 to 800 kcals per day can prevent starvation induced ketosis, proteolysis and gluconeogenesis; the reduction of leucine turnover in starvation is most likely the result of reduced protein synthesis; and the nitrogen sparing effect of carbohydrate is in part due to a decrease in branched chain amino acid catabolism.

Other studies using a universal eating monitoring system examine the palatability of different diets modified to contain less energy. It appears that individuals eat fewer calories when a highly palatable diet is modified to contain less energy, suggesting that low calorie analogs are effective in promoting weight loss. Added fiber to certain foods has also been shown to be effective in reducing calorie intake and in subsequent weight loss.

Studies in rats on the effect of exercise on metabolism and subsequent weight loss indicate that exercise increases endogenous lipoprotein lipase and decreases intracellular triacylglycerols in the heart and skeletal muscle, thus lipoprotein lipase may be responsible for the intracellular hydrolysis of triacylglycerols in muscle during exercise.

Studies on the fat substitute sucrose polyester (SPE) indicate that SPE may be an effective agent for weight loss in obese subjects. SPE is a synthetic, calorie-free substance that cannot be absorbed by the digestive tract and looks, tastes, and smells like common dietary fats. One study

of SPE included 10 chronically obese patients first fed a normal diet and then switched to SPE for dietary fat. An average of 60 grams of SPE replaced conventional fat in the altered diet which equaled a reduction of approximately 540 calories a day. Data from this study show that total calorie intake, which included meals and snacks, fell by 23 percent with the SPE diets. The subjects were better able to reduce their total intake of calories during the SPE period, while at the same time demonstrating appetite satisfaction. Snacks were not increased. The patients' average weight loss was approximately 0.4 pounds per day over 20 days. They demonstrated also a 10 percent reduction in total plasma cholesterol, a 14 percent reduction in low density lipoprotein cholesterol, and a 10 percent reduction in triglyceride level. Thus, sucrose polyester not only helps in weight loss, but, by virtue of its effect on plasma lipids, may also retard atherosclerosis.

Certain plant foods, such as kidney beans and wheat, contain a substance that inhibits salivary and pancreatic amylase. This anti-amylase has recently been purified, marketed for weight control under the generic name "starch blockers," and proclaimed to reduce the absorption of calories from starch. Studies have compared, by use of a 1-day calorie balance technique, the effect of starch blockers on calorie absorption after a high starch meal. The starch blockers did not inhibit the digestion and absorption of starch calories.

Studies have shown that behavior modification may be the most effective form of therapy for managing childhood obesity, especially if both the parent and child adhere to behaviorally oriented programs. After 2 years of followup, 100 percent of the children who had their parents participating in the weight loss program remained nonobese, while only 50 percent of those children participating alone maintained their nonobese state.

Another investigator examined the effects of behavioral modification on exercise in girls between 5 to 8 years of age. Earning a nonfood reward with an activity increased energy expenditure with exercise by 34 percent. Energy expenditure for the subsequent 90-minute period after the activity increased by 27 percent above the baseline post exercise energy expenditure. Children of thin mothers were able to do more work/kg of body weight than children of obese parents.

The relationship of obesity to disease states such as diabetes, coronary heart disease, cancer, stroke and hypertension is an important area of research. According to recent studies, individuals with fat distributed above the waist are more likely to develop diabetes than are those individuals who carry most of their excess weight in the hips and thighs. Men as a group and those women who are predominantly upper-body-obese are at the greatest risk of developing diabetes. Women with lower-body obesity have the least risk. Most of the excess weight carried by women with upperbody obesity is due to overpacked fat cells. Data suggest that variations in body chemistry determine the body's response to dieting, and perhaps the development of diabetes. Changes in eating patterns cause the enlarged abdominal fat cells in the upper-body-obese women to release fatty acids into the circulatory system. This influx of fatty acids might inhibit the use of glucose by body tissues causing the levels

of glucose and insulin to rise, predisposing the person to diabetes. A contributing factor to high glucose and insulin levels may be also the small number of insulin receptors on the large abdominal fat cells of upper-body-obese persons.

A number of studies are investigating the relationship between obesity and hypertension, cardiovascular disease (CVD) and coronary heart disease (CHD). In the Hypertension Prevention Trial, overweight is a criterion to assess susceptibility to hypertension. Among hypertensives, blood pressure correlates with weight, and weight loss is usually associated with a decrease in blood pressure. A prospective epidemiologic study following 40,000 men and women for 10 years is evaluating the relationship of obesity, glycemia, physical activity and other traits--independent of the major risk factors to atherosclerotic cardiovascular disease.

A recent report of the relationship between relative weight and the long-term occurrence of CVD in the Framingham Heart Study cohort indicates that multiple logistic regression analyses show that Metropolitan relative weight (MRW)* on initial examination was related to the differences in the 26-year incidence of coronary disease, congestive heart failure, and coronary death in men, independently of age, cholesterol levels, systolic blood pressure, cigarette smoking, left ventricular hypertrophy, and glucose intolerance. Increasing relative weight in women was found to be associated with increasing coronary heart disease, stroke, congestive failure, and coronary and cardiovascular death. These data indicate that weight gain after the young adult years conveyed an increased risk of CVD in both sexes that could not be attributed either to the initial weight or the levels of the risk factors that may have resulted from weight gain. These results indicate the importance of obesity as an independent long-term predictor of CVD. In terms of mortality, the Framingham Heart Study data show a "U-" or "J-shaped" univariate relationship between total mortality from all causes and relative weight. Mortality rates rise well above the average at the underweight and overweight ends of the relative weight distribution. However, there is almost complete confounding of the effect of cigarette smoking and low MRW on mortality by the high proportion of cigarette smokers among the subjects with relatively low MRW. This study does support additional evidence that body weights in excess of those recommended as desirable by the 1959 Metropolitan Life Insurance Tables are associated with increased mortality. Thus, "slimmer is better" as long as underweight is not associated with a medical history of significant impairment and there is no evidence of calorie, protein, vitamin or mineral deficiency.

A recent study in obese subjects has shown that obese men overproduce low density lipoprotein (LDL), the most atherogenic lipoprotein. This metabolic abnormality could be the cause of increased risk for CHD in obesity. In addition, diet induced hyperlipidemia is being studied in

*The midpoint of the desirable weight range for medium build (Metropolitan Life 1959) was chosen as the reference weight for a given height. The MRW was computed for each subject by forming the ratio of his or her body weight to the reference weight for the particular height. This ratio is expressed as a whole number in percent.

nonhuman primates. Obesity, hypertension, cigarette smoking and behavior are the risk factors being studied for their modulating effect on diet-induced atherogenesis.

In studies of obesity and cancer, research is under way on the effects of high and low fat diets, reduced calorie intake, and hypothalamic induced obesity on serum hormone levels and the subsequent development and growth of breast tumors. The overall objective of this research is to determine the brain's role, particularly the hypothalamus, in the development and growth of mammary and pituitary tumors and to utilize this information to inhibit such development and growth.

Nutrition Education Research

Research to uncover better methods to educate persons on the role of nutrition and diet in health and disease involves a number of intervention programs and clinical trials supported by NHLBI, NICHD, AND NCI. In FY 1982, \$10,152,000 or 7 percent of the total nutrition expenditures supported activities with significant nutrition research components.

A number of projects to determine appropriate nutrition education methods for children and their parents are included in this special interest area. One study is testing the effectiveness of various processes to measure conceptual knowledge of food and nutrition among preschool children. Discrimination and puzzle solving tasks appear to be effective techniques for measuring knowledge of food and nutrition, whereas free word association techniques do not. Findings from this study will be used to develop a nutrition education program aimed at decreasing sugar consumption and increasing consumption of nutrient dense foods.

Another project on the development of positive health behavior in preschoolers investigates the antecedents of positive and negative health behaviors early in childhood with the aim of producing an effective health education program that will have a lasting effect on adult health behaviors. The group of 3- and 4-year-old children who receive nutrition education intervention twice a week will have their health behaviors assessed yearly for 2 years after the intervention in order to determine any effect on dietary knowledge and behavior. The baseline data on the antecedents for adult health behavior are also being used to design educational programs for the parents.

The causes, prevention, and treatment of obesity in children is an important research issue. As a result, nutrition education research projects attempt to develop appropriate behavior modification methods that may prove useful. One project that evaluates early family environment and parent/child interactions in regard to food and eating will provide a model teaching base for students of various disciplines who are involved in the care and education of overweight and obese children. Another project is designed to ascertain whether the teaching of eating or exercise behavior should receive the most emphasis in a home-based behavior program. A study to determine the effectiveness of training parents to implement behavior techniques designed to regulate their obese children's eating and exercise habits has demonstrated that parents can indeed be

trained to implement a behaviorally-based program to improve eating and exercise habits.

A related project is developing and evaluating a behavior modification program for families of obese children that consists of a program to train parents in general child management skills, and encourages behavior modification by the parents, even though the obese child is the target of the intervention. Other studies are evaluating diet management strategies for overweight children, as well as those for obese children with Prader-Willi syndrome. Sucrose induced behavior changes are also being measured as part of the later program.

A study entitled "Infant Feeding Problems Today: Implications for Nutrition Education" interviewed mothers of 1-year-old infants to determine the mothers' exposure to nutrition information and its relationship to their feeding choices. Results of the study indicate that breast-feeding mothers are more inclined to follow the advice of friends, classes, and literature. Pediatrician's advice was followed most carefully by mothers who fed formula to their babies, who introduced solids before age 6 months, or who had low-birth-weight infants. Data on how infant feeding practices relate to growth indicate that weight and length measurements of breast and formula fed infants were similar.

Another project involves developing teaching materials for independent instruction in basic nutrition facts and testing the efficacy of programmed nutrition educational packages. Data collected thus far indicate that this method is effective in teaching facts but not in guiding students in the practical application of these facts. A project entitled "Nutrition Education Via Telecommunications Satellite" is designed to compare the effectiveness of the following three methods of nutrition education for health professionals: videotapes plus regular classroom discussion sessions; videotapes and structured discussion via satellite; and videotapes and informal off-campus discussion sessions. Results from the study show that students involved in formal discussions with instructors either in the classroom or via the satellite demonstrated similar learning and satisfaction with the learning experience. Those students without access to instructors performed reasonably well, but were much less satisfied with the course and its content. From this study, it seems that some personal contact, either directly or by satellite between students and instructors, is desirable for a successful and satisfying nutrition education program.

A number of intervention trials dealing with hypertension control have a nutrition education research component. The Dietary Intervention Study of Hypertension (DISH) is a collaborative study of the effect of dietary modification, i.e., nutrition education for weight reduction and sodium control on blood pressure levels. DISH has a goal of determining what percentage of hypertensive patients who had been treated for 5 years would be adequately controlled after antihypertensive medication, under the following circumstances: (1) withdrawal of medication, no dietary management, (2) withdrawal of medication, decreased sodium intake/increased potassium intake, (3) withdrawal of medication, weight loss, or (4) continued stepped (medication) care. Data analyses indicate that the

highest success rates were in the obese weight-reduction group (59.5 percent) and the sodium restricted group, who had thin body weight status.

Another study on the nonpharmacologic control of hypertension examines the feasibility of withdrawing medications from "mild" hypertensives and maintaining satisfactory blood pressure using only weight control and sodium restriction regimens. Preliminary data suggest that blood pressure control can be maintained in a high proportion of these individuals with little or no medications, especially with weight reduction and decreases in alcohol and sodium intake.

Dietary measures to control or prevent hypertension are also being studied in hypertensive prone individuals. A feasibility Hypertension Prevention Trial has enrolled 800 men and women between 25 to 50 years of age with high/normal diastolic blood pressure. Several intervention efforts employing dietary means to control hypertension are being examined for their success in obtaining decreases in weight, salt intake, and blood pressure.

Two demonstration and nutrition education research projects related to hypertension are under way at the New Jersey Medical School; one will explore the possibility that dietary change and/or relaxation training will reduce or eliminate the need for medication in a hypertensive population. The second project is testing the hypothesis that nonpharmacological treatment for hypertension can be carried out largely by paraprofessionals and in nonclinic settings, such as the workplace and in community sites. Another demonstration and education study on hypertension includes five family practice centers located in demographically diverse communities in Virginia. Behavioral education programs directed at high risk patients/families will be assessed in terms of an appropriate reduction of salt intake and smoking cessation.

A number of community demonstration studies attempt to produce significant changes in health behaviors associated with cardiovascular risk, thereby reducing excess morbidity and mortality associated with cardiovascular disease. Some of these programs emphasize the mobilization of existing community resources while others attempt to establish new programs and activities. These studies provide information on enhancing program continuity, in addition to data on cardiovascular risk factor reduction.

Three community based programs testing the hypothesis that cardiovascular disease (CVD) risk factors can be changed and maintained through community organizations and education strategies include the Stanford Health Disease Prevention Program, the Minnesota Heart Health Program, and the Pawtucket Heart Health Program. The Stanford program involves media campaigns with publications on blood pressure control, television spots on weight reduction, and a multimedia smoking cessation program. The Minnesota program is testing various strategies to lower CVD morbidity and mortality in three communities in the upper Midwest. The Pawtucket program examines changes in the CVD risk factors with a high level of professional and organizational assistance versus a low level of professional assistance. The risk factors being considered are blood lipids, blood pressure, smoking, obesity, and physical fitness.

A 5-year study currently under way is designed to modify cardiovascular family risk through a tailored intervention program for families, a school screening program, a high school level cardiovascular curriculum, and a parent education program. This intervention program will attempt to demonstrate greater gains in CVD risk factor reductions for those persons with a positive family history of CVD.

Results from the nutrition education program, Foods for Health, sponsored by NHLBI and Giant Food Inc., reveal that it achieved its main objectives of communicating nutrition information to the consumer, determining the feasibility of implementing and evaluating a point of purchase program, and creating interest and awareness about nutrition in outside business organizations. Data on the mean adjusted correct responses to the nutrition knowledge questions revealed a greater gain in correct scores for the Washington study population where the intervention occurred as compared to the Baltimore control group; i.e., a gain of 10 percent for questions on the fat/cholesterol content of foods and a gain of 6.8 percent for those on the relationship between dietary fat and serum cholesterol. These scores were associated with sex, education, age and having a family member on a special diet. In general, females from the Washington population had a higher percent of correct responses, and Washington respondents had higher reported educational levels. The weekly sales of specific food items were monitored in order to detect any change in sales in relation to the nutrition messages made in Washington and Baltimore, respectively. No apparent differences in food sales could be attributed to the nutrition education intervention.

The CNRU's are also a significant focus for nutrition education research since their mission is to combine research, patient care, and public education activities, often in the form of community outreach programs.

Examples of the research under way at the CNRU's include projects to evaluate the effectiveness of various in-service programs with basic nutrition information, and to develop innovative teaching tools for children with juvenile diabetes that can be adapted to each child's age and preferred learning mode. Research to develop nutrition education programs useful to fostering proper nutritional habits in children and adults, both professional and nonprofessionals, is an important undertaking of the CNRU's.

Total Parenteral and Enteral Nutrition

Appropriate nutritional support for those individuals unable to ingest, digest, or absorb foods is essential in order to permit normal growth, development and maintenance of health. Research continues therefore to examine and define the special nutrient needs of patients requiring total parenteral or enteral nutrition. DRR, NIADDK, NIGMS, NICHD, NCI, NIA, NHLBI, NIAID, and NINCDS supported \$8,801,000 or 6 percent of total nutrition research in this area.

Research on the parenteral requirements for amino acids in premature infants of various gestational ages indicates that the requirement for each amino acid is defined as that amount that produces a serum

concentration within 95 percent confidence limits of the 2-hour post-prandial serum concentrations observed in normal infants. In addition, the quality (fat versus carbohydrate) and quantity of the parenteral caloric supply to premature infants is being examined in terms of nitrogen retention. Newborn hyperglycemia induced by parenteral therapy, as well as the metabolism of intravenously administered lipid emulsions are also being studied.

In one study of neonatal hyperglycemia, investigators have found that low-birth-weight premature infants manufacture their own glucose even during constant glucose infusion. Infants weighing less than 1000 grams (26-29 weeks) all had glucose production rates less than 3.5 mg/kg/min. The more immature the infant, the lower the glucose turnover rate. These findings indicate that impaired utilization of glucose may be the major determinant of hyperglycemia in premature infants who receive parenteral glucose infusions. Plasma glucose levels ranged from 67 to 173 mg/dl and glucose production rates from 0.14 to 22.3 mg/kg/min.

In order to assess whether differences in the energy intake of premature infants primarily influence the rate of weight gain or the body composition of gain, one study is feeding two groups of infants equal volumes of formula with the same protein concentration, but different energy densities. Preliminary data suggest a similar rate of gain in both groups, thereby suggesting differences in the body composition. The investigators hypothesize that the higher energy intake will lead to a greater fat content of weight gain, and consequently a greater energy cost of growth.

Studies of lipid clearing in parenterally fed pre-term infants are measuring the activity of extrahepatic and hepatic-derived serum post-heparin lipolytic activity. Since heparin-released lipase activity is a direct indicator of total lipid activity, a decrease in lipase activity may potentiate the slower clearance of intralipid found in very low-birth-weight infants.

In terms of studies on enteral nutrient therapy in infants and children, the efficacy of nocturnal enteral glucose therapy in children with glycogen storage disease is being investigated. As a substitute to the current therapy of giving frequent high carbohydrate feedings during the day and a constant nocturnal nasogastric drip of glucose, investigators are looking at the effect of corn starch given every 6 hours. Thus far, they have demonstrated improved control of the aberrant metabolic status.

In order to understand the mechanism of food protein intolerances in infants, intestinal epithelial events (developmental changes in intestinal permeability to protein) are being examined in infants enterally fed lactose. It is hypothesized that lactose in breast milk is required as a source of galactose for glycosylation of epithelial glycoproteins and glycolipids. Studies in rabbits have shown that lactose concentration in milk and mucosal lactase activity in suckling rabbits correlates with the intestinal epithelium sensitivity to ricin, a toxin similar to soy protein lectin that binds to galactose residues. Lactose in breast milk, through its role in membrane glycosylation therefore may exert an influence on

mucosal uptake of milk proteins, as well as on trophic hormones such as insulin and epidermal growth factor, and on membrane stability.

Additional studies in infants consider the effect of cysteine and taurine in TPN given to infants; the metabolic fate of fat emulsions; and the amino acid and nitrogen balance with varied protein and energy intakes.

Studies on amino acid and nitrogen balance indicate that the branched chain amino acids, leucine, isoleucine and valine serve as biochemical regulators and precursors in such metabolic reactions as cholesterol synthesis, protein turnover in skeletal muscle, oxidative energy metabolism in muscle, gluconeogenesis, insulin secretion and urea formation. These amino acids therefore are being studied in the treatment of protein wasting found with trauma and sepsis, and hepatic encephalopathy. Data indicate that the effect of leucine and its keto analogue alpha keto isocaproic acid on protein conservation and protein synthesis may prove helpful in the treatment of portal-systemic encephalopathy, renal disease, diabetes, and trauma.

Studies of the nutritional support of patients, especially those with trauma and burns, have shown the benefit of providing 25 percent of the calories as protein and the need for first meeting the caloric requirement. It seems that malnutrition is the major contributing factor to the defects in phagocytic function leading to infections in such patients. In addition, severe opsonic deficiencies magnify these adverse defects. These patients also have an increase in glucose production and glucose flow with adequate insulin, as well as a sustained hypermetabolism and negative nitrogen balance causing severe weight loss. The underlying mechanisms of these changes and the necessary nutritional support to sustain life in these patients continues to be investigated.

The nutritional support of cancer patients is an important area of research which tests the hypothesis that the administration of TPN is more effective than normal hospital regimens in maintaining adequate nutritional status and that it does not adversely affect tumor control. A number of clinical studies as well as animal studies attempt to assess the effectiveness of TPN in maintaining the immune response and thereby lessening or moderating the complications associated with cancer treatment.

In animal studies, the hypothesis that a tumor induced amino acid imbalance is responsible for some of the tumor's effects on the host is being investigated through the administration of five parenteral diets containing different amino acid mixtures.

In addition, prospective trials of the use of TPN as an adjunct to radiation, surgery and aggressive chemotherapy are under way. One study is evaluating the benefits and complications of nutritional support to children receiving multimodal treatment for stages II to IV Wilms' tumor. Other studies examine the importance of nutritional rehabilitation in head and neck cancer, the efficacy of multimodal therapy in operable esophageal carcinoma, and the prevention or reversal of malnutrition in neuroblastoma.

The prolonged use of some total parenteral nutrition solutions has been shown to lead to such complications as bone disease in some patients. They appeared to have deficient serum levels of parathyroid hormone and the active vitamin D metabolite, as well as excessive urinary calcium excretion. Data has shown that reducing concentrations of calcium and protein led to decreased calcium excretion. More research on the mechanisms involved in metabolic bone disease is warranted.

Maternal Nutrition

The nutritional status of the mother affects the growth and development of her child, as well as her own health and well-being. Research in FY 1982 with an emphasis on maternal nutrition, totalled \$7,553,000, or 5 percent of the total nutrition expenditures. NICHD, DRR, NIADDK, NIDR, NHLBI, NIAID, NINCDS, and NCI supported this research.

Research in this area includes studies on: the relationship of maternal nutritional status to reproductive function; nutritional requirements of women during pregnancy and lactation; the relationship of maternal nutrient intake to fetal outcome and subsequent infant growth and development; placental transport of nutrients from maternal to fetal circulation; the causes and potential nutritional therapy for intrauterine growth retardation; and the various components of human milk.

Since a reduction in the dietary intake of energy and/or protein during pregnancy has been shown to be associated with fetal growth retardation, a number of longitudinal studies have attempted to ascertain the optimal nutrient requirements of the maternal-fetal unit. In addition to requirements for energy and protein, the requirements for vitamins, minerals and trace elements are under study. Data on the requirements for vitamin A, for example, reveal that maternal vitamin A serum levels fluctuate and vary with intake, but the exact mechanisms of control of these levels, placental transport, and fetal utilization of the vitamin remain unknown. Placental transport of vitamin A increases when the maternal stores are low, while high maternal stores suppress transport. Fetal metabolism of retinol appears to be specific and somewhat different than that of the mature animal. Quantitative determinations of retinol metabolism and kinetics in the maternal-placental-fetal system will facilitate the estimation of maternal, fetal and neonatal requirements and aid in the prevention of fetal losses and neonatal disease associated with inappropriate vitamin A intakes.

Vitamin A in excess or deficient quantities early in the gestation of animals has been shown to cause anomalies that frequently involve the eye. The form of vitamin A transferred to the developing fetus of different gestational ages, its deposition in various fetal tissues including the eye, and the mechanism of placental transport are being investigated in rats. This research will provide insights into the influence of maternal vitamin A status on normal fetal development of ocular tissue and on subsequent visual function.

Since vitamin A transport, storage and utilization are highly dependent on protein, the study of vitamin A metabolism in the maternal-fetal

neonatal unit also includes examination of the effects of protein intake. Dietary levels of vitamin A significantly affect protein metabolism, thus the protein requirement may vary depending on the vitamin A intake. Moreover, the vitamin A requirement is likely to vary with protein intake.

A rat model is also being used to study the degree of fetal growth that can be supported from maternal lean tissue catabolism. Studies of 24-hour 3-methyl histidine excretion have shown that maternal muscle tissue breakdown is a function of maternal diet, and that the metabolic needs for fetal growth are not met from maternal muscle tissue breakdown.

The means by which nutrients pass from the mother and her fetus are indeed complex. The placenta must provide the human fetus in late gestation with 10 mmoles/kg/day of amino acids for tissue anabolism, 20-25 mmoles/kg/day for nitrogen catabolism and 40 mmoles/kg/day of glucose. Studies on the mechanisms responsible for the net transfer of these large quantities of nutrients have revealed that the mammalian placental microvillus membrane capacity for glucose uptake exceeds fetal needs by a factor of sixteen. In addition, a glucose transport protein, with a molecular weight of 52,000 and associated with actin, has been identified to mediate the transport of glucose from the mother to the fetus.

Other research has shown that in late gestation, approximately one-third of the maternal glucose production is utilized by the placenta and a lesser amount by the fetus. In response to maternal hypoglycemia or fasting, the conceptus (placenta plus fetus) reduces its utilization of maternal glucose and increases the production of endogenous glucose. However, the decreased utilization of maternal glucose is associated with decreased fetal growth.

Iron transfer across the placenta is also vital for fetal growth. During pregnancy, the fetus accumulates large amounts of iron in order to support erythropoiesis, and maternal iron must be actively transported against a trans-placental concentration gradient. Investigations using a guinea pig model have shown that ferric placental iron moves from the maternal to the fetal circulations by passing through endothelial cell junctions, possibly with a low molecular weight carrier protein; maternal transferrin releases iron at the cell surface and does not cross the placenta; and fetal iron does not cross the placenta into the maternal circulation but regulates the transport of maternal iron into the fetal circulation.

Studies on calcium placental transport have isolated and purified human placental-calcium binding protein (HCa BP) with a molecular weight of 150,000 and 27 percent acidic residues of aspartate and glutamate. HCa BP is saturable at concentrations of Ca^{++} above 4 mM; cellular localization studies have shown that the calcium binding protein increases in concentration during gestation and is primarily associated with the maternal face of the chorioallantoic placenta and the uterine wall.

In general, fetal needs for specific levels of nutrient substrates can be met by the usual ranges of the nutrients encountered in the maternal-placental circulation. Studies, however, are investigating fetal growth and nutrient requirements that take into account the differential genetic

composition of mother and fetus. Genotypic exigencies dictate fetal demands for nutrients such as copper, manganese, pyridoxine, and biotin that exceed the maternal-placental circulation supply. Deleterious fetal development can be avoided if the nutritional demands of the aberrant genotypes are met by augmenting the maternal diet with specific nutrients. The basic discovery in the realm of intrauterine-genetic-nutrient interactions paves the way for nutritional therapy during fetal life for certain inborn errors of metabolism and other kinds of extreme nutrient dependency. Diseases which have been fatal in the untreated newborn can be transformed into a harmless condition by safe and effective treatments prior to birth. Such treatment obviates the need for prenatal diagnoses and its attendant risk to the fetus.

Research continues on elucidating predictors of intrauterine growth retardation (IUGR) which affects approximately 100,000 pregnancies per year in the U.S. Its etiology is multifactorial in nature and involves maternal nutritional status and maternal nutrient intake during pregnancy, placental circulation and nutrient transfer, maternal smoking and socioeconomic status, and maternal fetal endocrinological status.

The role of polyamines in the maternal circulation as physiological indicators useful to differentiate normal and abnormal pregnancies is being investigated. Polyamine levels increase in the amniotic fluid as a function of gestation, presumably as a reflection of rapid fetal growth. The analysis of the amniotic fluid polyamine levels may provide an important marker for fetal problems such as IUGR.

An ovine model of IUGR by induced placental insufficiency or by maternal dietary restriction (20 percent of required protein and 50 percent of required calories during the third trimester) is being used to investigate differences in fetal body composition resulting from IUGR. Another ovine model has shown that infusion of a 4 percent glucose and 6.8 percent amino acid solution directly into the fetal stomach during the period of maternal dietary restriction significantly increases birth weight and crown/rump length when compared to unsupplemented fetuses of nutritionally deprived ewes. These investigators have also shown that during maternal dietary restriction, the upper body of the fetus receives substantially greater blood flow than the lower body which may be important in protecting growth of upper body organs (brain and heart). Research to test intrauterine nutritional therapy in humans will likely be forthcoming.

Research on infantile respiratory distress syndrome (RDS) is also a priority since RDS is the single most frequent cause of death during the neonatal period. A small but important fraction of the risk deals with the nutritional status of the mother, which along with steroid therapy is being studied as a possible means of reducing the risk of premature birth and consequent risk of RDS. Other studies investigate maternal protein intake and mental retardation in the newborn, as well as the effect of dietary deficiencies and ethanol intake on neural development.

In terms of the impact of disease states or conditions of women on the fetus and newborn, studies continue on maternal phenylketonuria, diabetes

in pregnancy, pica, and pregnancies complicated by hypertension and renal disease.

Factors affecting lactation and immune properties of human milk are under study in order to establish the best possible conditions for infant feeding. The effects of diet, smoking and drinking on lactation are being investigated as well as the bioenergetics of fasting and lactation.

Additional highlights on human milk research are included under the special interest area on "Child and Infant Nutrition Research."

Nutrition Education for the Public

An integral part of the NIH nutrition program is the translation of research results into practical information for the public. The NCI and NHLBI have specific mandates for information and education. In addition, work is supported by NIADDK, NICHD, NEI and the Nutrition Coordinating Committee office. In FY 1982, \$5,897,000 or 4 percent of the total nutrition program supported projects with a significant effort in nutrition education for the public.

Nutrition information is disseminated through specific NIH publications and fact sheets available from the various Institutes' information offices, Public Service Announcements (PSAs), the NIH lecture series "Medicine for the Laymen," films or videotapes, and responses to public inquiries. In FY 1982, the nutrition publications available to the public included: Questions about Weight, Salt and High Blood Pressure, Fact Sheet Hyperlipoproteinemia, and various "Eater's Almanacs," (NHLBI); "NIA Age Page: Food: Staying Healthy After 65," (NIA); "Food Allergy," (NIAID); and "Snack Facts," (NIDR). The USDA/DHHS publication, Nutrition and Your Health, Dietary Guidelines for Americans, is also available to the public from the Consumer Information Center, Pueblo, Colorado.

One public service program, entitled "Living with Aging" and done in collaboration with the NIH and Peoples Drug Store, is providing the elderly and their families with important health promotion information. "Food for Life After Age 65" and "Taking Care of Your Teeth" are two of the eight free brochures that are being displayed in all of the Peoples' 525 drug stores in 14 states and the District of Columbia. These brochures, designed and printed by the drug store, are based entirely on the existing Age Page publication by NIA. The first draft of a new Age Page on "Dietary Supplements" has been prepared and will be available in the near future.

Two new nutrition publications soon to be available to the public are "Facts About Nutrition," a publication of general nutrition information on the various nutrients, i.e. their functions, requirements, etc., and "Facts About Obesity," a publication that explains obesity in terms of causes, prevention, and appropriate treatment. These publications will be available from NIADDK.

A collection of articles about NIH research developments is compiled by the NIH Office of Communications in the publication entitled NIH News

and Features, which is made available to various members of the press and scientific journalists, as well as the general public. Approximately 8 to 10 percent of its content contains nutrition research activities and highlights. The NIH lecture series "Medicine for the Laymen," now in its fifth year, included a lecture on "Behavior Patterns and Health." This lecture examined six common lifestyle factors--dietary patterns, exercise, alcohol use, cigarette smoking, stress and sleep patterns--and their relationship to health and diseases, such as heart disease, cancer, stroke, diabetes, etc. This series is videotaped for possible use on public television.

A number of studies are under way to evaluate the various means of educating certain segments of the general public about different aspects of nutrition. These studies include investigations to determine the effectiveness of various procedures to measure conceptual knowledge of food and nutrition among preschool children, to develop a comprehensive health education curriculum stressing health behaviors in preschool children, and to train parents in ways to manage their children's nutritional intake. It seems that children of parents who had received additional child management training maintained their weight loss better than other children. These projects are described in more detail under the special interest area on "Nutrition Education Research."

Nutrition education and information programs are also integrated into various cancer and heart disease education programs. Efforts are under way to educate the public on the role of diet and nutrition in cancer etiology and prevention, as well as in the treatment and rehabilitation of the cancer patient. The Diet, Nutrition and Cancer Program, NCI, has developed and distributed a number of pamphlets and handbooks to advise cancer patients on the role of nutrition and cancer therapy. Work with the Candlelighters also continues in order to develop resource material for the child with cancer. Community based programs that educate the public on cancer also include nutrition information as a major component.

Programs also continue to translate fundamental research results in heart disease into practical suggestions. The role of nutrition in good heart health was explicitly stressed in the "Foods for Health" program initiated by NHLBI in cooperation with Giant Foods in FY 1978. Supermarket shoppers received free information on the relationship of diet and coronary heart disease through publications known as "Eater's Almanacs." Requests to reprint the almanacs continue to be received in FY 1982. The final report on this project has been completed and the findings are described in the special interest area on "Nutrition Education Research."

The NCC and the NCC Subcommittee on Nutrition Education again in FY 1982 served as consultants in the production of the sequel "Eat Well, Be Well II," produced by Amram Nowak Associates under a contract with the Metropolitan Life Foundation. This sequel included cooperation from government, industry, and the scientific community in a nutrition education endeavor. It is described in detail on pages 134-7 of this report.

In addition, the Subcommittee on Nutrition Education developed a comprehensive program of nutrition activities that were carried out at the

NIH for all employees during National Nutrition Month, March 1982. As part of these activities, it conducted a nutrition education workplace intervention project which is described in detail as part of the sub-committee's FY 1982 activities presented on page 139 of this report.

Another service provided by all the Institutes and by the NCC is the handling of public inquiries, both by mail and telephone. Information specialists are available during working hours to answer any questions--lay or professional--not only on nutrition, but also on all research topics within the purview of the NIH. In addition, the NCC maintains a full-time office staff to provide support to the committee and to serve as a focal point for nutrition information. The NCC office responds to inquiries from the scientific community, the media, and the concerned public.

Nutrition and Aging

Nutrition is certainly one of the influential environmental factors that exert chronic influence on the aging organism. Much of the research on nutrition and aging considers whether nutritional needs change significantly beyond the middle decades of life and, if so, what specific nutrients are involved. In FY 1982, NIA, NHLBI, NEI, NIADDK, DRR, NINCDS, and NCI supported \$5,861,000 or 4 percent of total nutrition research for studies in this area.

Laboratory and clinical studies are under way to examine the effect of aging on nutrient requirements, absorption and metabolism, as well as the effect of diet on the natural history of diseases common in the elderly such as osteoporosis, diabetes, blindness, cancer, hypertension and atherosclerosis.

Several animal studies attempt to look at the various phenomena related to aging and nutritional parameters. Investigators have reported that some strains of rats and mice live considerably longer when their diets are restricted either by feeding them every other day, or by reducing their calorie and/or protein levels each day. Recent studies at NIA's Gerontology Research Center (GRC) indicate that diet restricted rats not only live longer but are also smarter and healthier than rodents allowed to eat freely. For example, the older diet restricted rats learned complex mazes about as well as young rats, and much better than aged rats fed freely. Their kidney function was similar to that of young rats and much better than the freely fed older rats.

In terms of the effect of different schemes of dietary restriction on aging and longevity, it appears that a reduction of protein and calories is the most effective dietary scheme for prolonging life in rats. These data also suggest that food restriction begun in adult life is almost as effective in extending life as is life-long food restriction.

Caloric restriction alone retards bone growth and alters bone composition, i.e., bone is less dense, less well calcified, and has a higher lipid content. In addition, these rats do not have the normal age-related increase in calcitonin, the hormone that acts to inhibit bone resorption.

In order to more clearly understand the biological mechanisms by which caloric undernutrition retards immunologic aging and therefore extends lifespan the following five hypotheses are being studied in animals: possible shifts in lymphocyte subpopulations; effects on intrinsic age-related biochemical lesions in lymphocytes; slow down of age-related changes in thymic differentiation; changes in the micro environment with age; and amelioration of the autoimmunity of aging. Dietary restrictions are instituted at different periods of the lifespan (weaning, 12, 18, or 24 months) with particular emphasis on adult-initiated restriction. The diets are modified by varying protein levels over the lifespan, replacing sucrose with dextrose, adding retinoids, and balancing or restricting fat intake among groups differing in caloric intake. Psychological testing will be done to determine if undernutrition without malnutrition affects behavior, i.e., intelligence. Brain morphology, lifespan parameters, growth rates, body weight parameters, and disease frequencies with an emphasis on cancer and immune complex diseases will be determined. Methods to test the various hypotheses include enumeration and functional assays of B cells, T cell subsets, and determinations of cyclic AMP and GMP and their generating enzymes, energy change, adenosine deaminase and kinase 5'nucleotidase, nucleotide phosphorylase, catalase, mitochondrial respiration, DNA damage following UV and gamma injury, etc.

In an attempt to clearly define the various parameters with aging that are most conducive to a reduction in the risk of spontaneous tumors, studies in rats are investigating the hypothesis that dietary practices early in life moderate tumor susceptibility throughout an individual's lifetime. Results have shown that animals permitted to eat freely had a significantly shorter lifespan and more tumors over the same period of time than the experimental group of rats on specific diets. An animal model used to describe the conditions that contribute to the susceptibility of spontaneous tumors of the anterior pituitary gland has shown an unusually high growth rate associated with a high level of the food consumed and converted into body mass during early life, and a high intake of protein relative to body weight during early life. The emphasis of much of this research is on the dietary influences in the aging immune apparatus with special interest on immunologic suppressor effects, as well as on the efficacy of adult onset dietary restriction as an inhibitor of spontaneous carcinogenesis.

Other studies in animals are testing the hypothesis that subeffective brain damage (or effective damage) in younger adult rats yields symptoms of catecholamine deficiency during old age. The question of whether special feeding regimens can reduce or prevent catecholamine deficiency is being investigated.

The development of atherosclerosis, coronary heart disease, stroke, hypertension and blindness with age are common concerns in geriatrics research. One study on the effects of a fish oil diet on the natural history of coronary and cerebral atherosclerosis in monkeys has provided strong evidence that the atherosclerosis sparing effect of the fish oil is due to the preferential incorporation of that fatty acid into the platelet membrane phospholipids, which changes platelet function in ways favorable to diminishing atherosclerosis.

Accumulation of fluorescent pigmented material, lipofuscin, in the retina is a usual consequence of aging. Lipofuscin is thought to originate from the oxidation of cell products such as unsaturated lipids, including polyunsaturated fatty acids, and vitamin A. Studies in rats indicate that high dietary levels of vitamin A greatly increase the rate of accumulation of lipofuscin in the retinal pigment epithelium, and that this phenomena is further exacerbated when vitamin E is limited. The level of vitamin E as a natural antioxidant may impede the rate of oxidation in ocular tissue and hence influence the rate at which lipofuscin accumulates.

Studies of glucose intolerance and diabetes in elderly subjects have shown that basal glucose production is approximately 10 percent less than that in young adults. Glucose carbon recycling and glucose oxidation estimated from $^{13}\text{CO}_2$ excretion, however, did not differ significantly between the two age groups when expressed as a percent of glucose production. Furthermore, elderly adults were capable of suppressing hepatic glucose output to the same degree as young adult controls when infused with various concentrations of exogenous glucose. These studies demonstrate that reduced glucose tolerance seen in the elderly is due to an impairment in the sensitivity of peripheral tissues to glucose uptake.

In terms of changes in the digestion and absorption of nutrients with age, the changes in the bacterial flora in aging individuals has been shown to decrease the resistance to pathogenic microorganisms which results in a decreased absorption of essential nutrients leading to malnutrition. This process has been reversed by antibiotic treatment.

Nutrition Education for Professionals

Nutrition education activities for the various health professionals, i.e., physicians, research scientists, nutritionists, registered dieticians, nurses and other support staff, are critical to the advancement of nutrition sciences. The adequate dissemination of new research findings is important to practical applications in the field. NCI and NHLBI have specific mandates for providing education programs to the professionals, while NIADDK, DRR, NIA, and NICHD also supported nutrition education activities for professionals. In FY 1982, support in this area totaled \$5,014,000 or 3 percent of the overall nutrition program.

The mechanisms used by the NIH to provide nutrition research information to the professional include publications in various medical and scientific journals such as the Journal of the American Medical Association, American Journal of Clinical Nutrition, Journal of Pediatrics, Journal of the National Cancer Institute, Journal of Clinical Investigation, New England Journal of Medicine, Journal of the American Dietetic Association, and many others. For example, the November 1982 supplement to the American Journal of Clinical Nutrition, volume 36, number 5, contained the proceedings of the symposium, "Evidence Relating Selected Vitamins and Minerals to Health and Disease in the Elderly Population in the United States," held in May 1982.

Other nutrition publications published primarily for professionals by various NIH Institutes as well as the NCC office include: three publi-

cations, "Obesity: Does it Modulate Infectious Disease and Immunity," "Overview of Nutritional Status in the United States," and "National Nutrition Policy in the United States" that appeared in Nutrition in the 1980s, Constraints on Our Knowledge (Alan R. Liss, Inc., New York); two publications, "A Model Workshop for Nutrition Counseling for the Reduction of Cardiovascular Risk Factors," and "A Manual in Nutrition Counseling for the Prevention of Coronary Heart Disease," prepared jointly by NHLBI and the American Heart Association, are intended to enhance the interviewing and counseling skills of the nutrition counselor. In addition, the tenth revision of the Recommended Dietary Allowances (RDA's) and a manual entitled How To Use The RDA's are being prepared through a contract with the Food and Nutrition Board, National Research Council (NRC) of the National Academy of Sciences (NAS).

An important mechanism for imparting nutrition information to the professional is through various workshops and conferences. In FY 1982, 13 conferences were sponsored by NCI, NHLBI, NIADCK, NICHD, NIA, NIAID, NEI, FIC, and the NCC. They are listed on page 33 of this report.

In addition, representatives from the Institutes are members and provide support to international groups such as the International Vitamin A Consultative Group (IVACG). This group, which is composed of policymakers, scientists, and representatives of funding government agencies, seeks to reduce blindness due to malnutrition through an increased awareness of the problem and various intervention programs. IVACG, with support from NEI, is preparing for publication a manual on Biochemical Methodology for the Assessment of Vitamin A Status and a companion volume of Reprints of Selected Methods for Analysis of Vitamin A and Carotenoids in Nutrition Surveys. The work of this group is aimed at the education of the professional in the control of blindness due to malnutrition.

The seven Clinical Nutrition Research Units (CNRU) have active educational programs for professionals in accordance with one of the three stated objectives of a CNRU: "To strengthen training environments in order to improve the education of medical students, house staff, practicing physicians, and paramedical personnel in clinical nutrition." For example, a new 10-hour elective course in nutrition is being offered to the second year class of medical students at the Cornell University Medical College with assistance from Memorial Sloan Kettering Cancer Hospital's CNRU team.

An important multi-institutional effort to assist and encourage education in clinical nutrition has led to the establishment of a "Regional Center for Education in Clinical Nutrition in the New York-New Jersey Metropolitan Area." This center serves as a resource, planning and evaluation agency for faculty in 10 medical schools, 5 dental schools, 2 schools of osteopathy and major teaching hospitals in the region. The center's staff, in cooperation with faculty members, obtains information on the current status of nutrition in the curriculum, on the availability and effectiveness of nutrition training programs in the clinical years, and on the quality of audiovisual and printed nutrition materials. They also have developed a "lecturers bank" for teaching purposes and work with the physicians and other health professionals in order to develop

both comprehensive and specialized clinical electives in nutrition. Periodic surveys will determine changes in the extent, quality, and effectiveness of nutrition teaching programs.

International Nutrition Research

International nutrition research continues to be important in advancing nutrition science, in assisting in the solution of food and nutrition problems throughout the world, and in strengthening our international relationships. International nutrition research includes studies that utilize the special talents and different environments available in studies conducted in the less developed countries by U.S. or foreign scientists. Studies are also conducted by foreign scientists working in the U.S. or other countries of the developed world. In FY 1982, NICHD, NCI, NHLBI, NIADDK, NIEHS, NIAID, DRR, and NEI supported international nutrition research for a total of \$2,245,000 or 2 percent of total expenditures in nutrition research.

In the absence of a solution to the maldistribution of the world's food supply, research on common states of undernutrition, such as protein-calorie malnutrition, and iron and vitamin A deficiencies, attempts to determine how these states affect the growth, development and overall health status of individuals. Research also examines the individuality and adaptation processes of various populations under certain conditions in order to develop the appropriate nutritional support.

Undernutrition, superimposed on various disease states, particularly diarrheal infections which cause impaired utilization and loss of nutrients, is the primary cause of death of children under the age of 5. One study of protein/calorie malnutrition (PCM) in children, under way in Guatemala, is examining serum factors responsible for the opsonization of bacteria. Deficiency of complement and of complement-mediated opsonins, known to occur in malnourished hosts, may play a role in the high incidence of fatal gram-negative septicemia in acute malnutrition. The effect of dietary therapy alone or dietary therapy plus replacement of complement in the form of fresh-frozen AB/Rh+ plasma on serum complement levels and opsonin activity is being assessed in these children with PCM. Results from the study indicate that dietary therapy with the replacement of complement in the form of fresh-frozen plasma increases functional complement activity in the serum of undernourished children. This plasma has also been shown effective in increasing complement activity in chronically ill adults suffering from protein calorie malnutrition in developed countries.

Another study of deficiency states in preschool children is under way to assess whether a low dietary intake of zinc contributes to poor linear growth velocity. Preschool children of Mexican-American ethnic origin were given a 10 mg/day supplement of dietary zinc; only children in the lowest 10 percent height for weight were included in the study. Only boys appeared to have a significant increase in linear growth velocity with the supplement.

Research on zinc deficiency in young men revealed that RNAase activity is significantly increased in the parotid saliva and blood plasma during zinc depletion, and returns to normal with zinc repletion. Leukopenia with relative lymphocytosis is also present in zinc deficient men, indicating that the effects of zinc on man's immune function also deserves attention.

Iron deficiency and iron deficiency anemia is another area for international investigation. Research on iron deficiency has shown an association between increased red blood cell membrane stiffness and decreased red blood cell survival in iron deficiency primarily due to decreased membrane viscoelasticity. Iron deficient red blood cells have an increased susceptibility to peroxidation and spontaneous crosslinking of membrane protein and lipid.

Studies on the effects of anemia versus tissue iron deficiency on work performance in rats employed exchange transfusions to control the hemoglobin concentration in both tissue iron deficient and control rats. Results from this work indicate that defects of $\dot{V}O_2$ max and aerobic work capacity result primarily from anemia, while endurance capacity depends on the capacity of muscle mitochondria to utilize oxygen and produce ATP.

The role of vitamin A status in blindness frequently associated with measles among children in developing countries is being investigated in India. Appropriate methods to assess vitamin A status are being tested in the field. Collaborative centers for research on cataracts and nutrition's role in their development are also planned for India.

One new test recently developed to assess vitamin A status of children as young as 4 years is a rapid dark adaptation test. The test involves matching the intensities of color disks to cone function (not rod function) so that under dim lighting conditions, the ability to separate the different colored disks depends on rod function alone. Some studies have shown that protein status affects the ability of the retina to utilize vitamin A. In patients with protein deficiencies, studies have shown that dark adaptation is uncorrectable with vitamin A or zinc alone. In such patients dark adaptation response did not improve until protein was repleted. A new approach to the assessment of vitamin A status seeks to identify and quantitate on a population basis the prevalence of subclinical vitamin A deficiency when biochemical and clinical signs are not present. Such an approach will provide a quantitative method for estimating the magnitude of the "at risk" population and the effectiveness of intervention programs to decrease the number of people "at risk" of developing clinical vitamin A deficiency.

In subjects with chronic hemolysis due to Mediterranean type glucose-6-phosphate dehydrogenase deficiency, vitamin E supplementation appears to significantly increase hematocrit and hemoglobin levels, prolong red cell survival, and reduce reticulocyte counts. This finding was also apparent in a group of Israelis with glucose-6-phosphate deficiency.

Studies on the composition of breast milk and milk intolerances continue in order to increase our knowledge of the effects of infant feeding

practices on subsequent development. The composition of breast milk from Mexican mothers is being compared with that from Houston mothers while taking into consideration differences in ethnic backgrounds, exposure to agricultural and industrial toxins, pathogens, and dietary intake. This study also includes a longitudinal epidemiological study of breast-fed and bottle fed infants in order to evaluate the stability of protective factors of human milk with regard to refrigeration, freezing, and pasteurization. The possibility of passive protection (in breast-fed infants) from gastroenteritis due to enteropathogens will be examined. Results from this research will help to develop guidelines for banking and storage of human milk.

The prevalence of milk intolerance due to lactase deficiency in the Inuit Eskimos and Indians of Canada is shown to be approximately 73 and 60 percent, respectively. By ascertaining levels of vitamin D and its metabolites in Eskimo and Indian children, the investigators will relate the prevalence of milk intolerance among these groups to the effectiveness of the Canadian program of milk fortification with vitamin D.

Investigations in Costa Rica and Colombia are analyzing human fertility patterns in relation to the duration of breast feeding, as well as to proxies of nutritional status such as sharecropping and land tenure. Additional work on the relationship of subsistence patterns, dietary intake, and nutritional status of inhabitants, particularly children up to 5 years of age, is being carried out in the Sudest Island and the Louisiade Archipelago of Papua, New Guinea. Malnutrition in children has been reported to be approximately 96 percent in the Sudest Island; rates of malnutrition appear to follow cultural rather than environmental boundaries. Preliminary findings suggest that changes in the subsistence patterns on the island from a reliance on the collection of wild foods and fishing to a heavy emphasis on the cultivation of starchy root crops have had a deleterious effect on nutritional status. Also, traditional proscriptions against feeding young children any animal foods are strictly followed in some areas of hyperendemic malaria. These areas also report the highest rates of child malnutrition. Data suggest that the plasmodium do not live within the red blood cells of hosts with a marginal nutritional status, therefore, these malnourished children may be partially protected from the disease.

A study in Kenya is making attempts to quantitate the negative effects of Schistosoma hematobium infection on nutritional status and to evaluate the benefits of oral antischistosome drug treatment on nutritional status.

One of the main avenues through which NIH supports international nutrition research activities is the U.S.-Japan Cooperative Medical Sciences Program and its Malnutrition Panel. Specific areas of research involve studies on the effects of changing dietary patterns on disease; the effects of malnutrition on lactation, reproduction, physical and mental development, and work performance; the interaction of nutrition, immune competence and infection; and the influence of environmental and host factors on nutritional requirements. Although the people in Asia remain the primary area of interest, research in other developing countries may

be included under the auspices of the U.S.-Japan Cooperative Medical Science Program and its Malnutrition Panel.

Since the primary diseases afflict persons in both the developed and the lesser developed countries of the world, international nutrition research examines cancer incidence in various populations, the prevalence of lipid disorders and the effect of diet on these disorders, and the relationship of these disorders to cardiovascular disease.

A number of epidemiological studies examine the possible relationship of diet and/or nutritional status on the incidence and natural histories of cancer. One study in Colombia is investigating the prevalence of cancer with geographical pathological findings, while a number of interdisciplinary investigations are looking at the nutrition related risk factors for the major cancers in populations from Japan, Yugoslavia, Finland, and in many U.S. cities. The demographic and clinical features of an Albino population in Tanzania are being studied in terms of their possible relationship to the high incidence of skin cancers. A clinical trial on the use of 13-cis-retinoic acid on the chemoprevention of skin cancer in this population is also under way.

A number of studies are examining the carcinogenic risks of chemicals to humans. Two studies involve N-nitroso compounds; one under way in the United Kingdom is attempting to develop analytic methods to determine the N-nitroso compounds in various foodstuffs, while the other under way in Canada is investigating biochemical and morphological changes in the development of liver cancer induced by diethylnitrosamine, 2 acetylaminofluorene, dimethylnitrosamine, and other hepatic carcinogens.

International nutrition research to look at environmental contaminants includes investigations on adaptive metabolic responses in gastrointestinal and pulmonary tissues to environmental xenobiotics. The influences of polybrominated biphenyl, polychlorinated biphenyl, and polychlorinated naphthalenes on biotransformation rates are being studied, as is the relationship between induction and the tissue level of xenobiotics. Intestinal biotransformation regulation by dietary factors is being evaluated in in vitro models and isolated intestinal sacs.

In the area of cardiovascular disease, a number of studies are under way in Israel, Canada, Puerto Rico, the USSR, Yugoslavia and the People's Republic of China. A cooperative agreement with Japan allows for experimental studies on the dietary prevention of hypertensive and atherosclerotic diseases. Epidemiological studies under way in the Lipid Research Clinics (LRC) are designed to generate internationally comparable information on plasma lipids and lipoproteins, cardiovascular risk factors, and demographic and nutritional status that will allow a comparison of the heart disease problem.

Data from the LRC in Jerusalem indicate that in native born 17-year-old army inductees, plasma cholesterol levels differ according to the country of parental origin. The highest cholesterol levels are seen in those with parents from the West, while the lowest levels were in those with parents from North Africa and Asia. Total fat, saturated fat, and

cholesterol intake correlated with the plasma cholesterol level. Such investigations provide important insights into the cardiovascular risk factor associations in diverse populations.

Also under investigation are the risk factors contributing to glucose intolerance; obesity, diabetes and adipose tissue development; genetic factors that contribute to obesity; inborn errors of carbohydrate metabolism; and the nutritional management of osteoporosis.



II.

NUTRITION COORDINATING COMMITTEE

Nutrition is an important, crosscutting program area within the NIH. For this reason, the nutrition program is coordinated through the Nutrition Coordinating Committee that operates out of the Office of the Director and is advisory to the Director. The committee is the focus for the review of nutrition research priorities and training, their coordination, and for the development of the NIH program in biomedical and behavioral nutrition research and training. This focus minimizes duplication of effort among the Institutes and identifies areas where research, research training and manpower development in nutrition need to be advanced.

COMMITTEE STRUCTURE

The Nutrition Coordinating Committee operates out of the Office of the Director and is advisory to the Director, NIH. The membership of the NCC consists of representatives from the 11 Institutes and the Division that support nutrition research. Additional NIH offices, other agencies of the Public Health Service and the Department of Health and Human Services, and the Office of Science and Technology Policy in the Executive Office of the President have liaison representatives to the Committee. As of September 30, 1982, the NCC was composed of the Chairman, 23 members and alternates, 1 consultant, 10 liaison representatives and alternates from interested offices within the NIH, and 9 liaison representatives and alternates from other Federal agencies. The mandate of NCC appears in appendix A.

The committee, established in 1975, reviews and comments on the plans, execution, and results of pertinent Bureau, Institute, and Division research efforts relating to nutrition in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. In addition to staffing the NCC, the office staff provides information requested by the Office of the Director, and represents NIH in numerous activities involving nutrition research at DHHS, the Office of Science and Technology Policy, other Federal and non-Federal agencies, industry, and professional societies. The NCC office also maintains information on national and international nutrition meetings and conferences.

NCC meetings are normally held once a month and are attended by the members, liaison representatives, and committee office staff. In addition to the regular business of the committee, special presentations on subjects of current interest to the NCC are frequently made by scientists from other agencies or groups. FY 1980 marked the beginning of the special Scientific Seminars in Nutrition presented during the last hour of each NCC meeting. These special seminars continued in FY 1982 with presentations made by extramural, intramural, and visiting scientists engaged in nutrition research at the NIH as well as scientists involved in nutrition research at other government agencies.

In addition to committee activities, a number of special activities were carried out through the NCC Subcommittee on Nutrition Education. The Subcommittee on Nutrition Education was restructured in March 1981 to include representatives from NCI, NEI, NHLBI, NIDR, the Clinical Center, the Office of Communications and the NCC Office.

COMMITTEE ACTIVITIES AND ACCOMPLISHMENTS

Scientific Seminars

In order to highlight research in nutrition, especially that research carried out by intramural scientists at the NIH, and to keep the NCC representatives informed of research developments in nutrition, the NCC inaugurated a program series called Scientific Seminars in Nutrition. The seminars are presented during the second hour of the monthly NCC

meeting. During FY 1982, the following eight Scientific Seminars in Nutrition were presented:

- 1) "Dietary Studies in Twins" was presented by Dr. Walter Nance, Department of Human Genetics, Virginia Medical College, at the October 22, 1981 NCC meeting. A summary of his presentation is given below.

Clinical studies of twins allow for the control of the genetic variation among individuals, as well as the environmental differences. Three research designs can be used with twins, i.e., the co-twin control study, the classical twin method, and the analysis of data from the families of twins. The co-twin control study can be either retrospective or prospective; the retrospective study identifies identical twins discordant for a particular trait or disease state. These twins are compared with respect to clinical findings or past history possibly related to the disease in question. This kind of study permits the identification of genetic influences on variables that appear to be environmental in etiology. One disadvantage is that the assignment to the control and treatment groups is by self-selection.

Prospective co-twin control studies, on the other hand, can incorporate the use of placebo treatments and double blinding into the experimental design. One such study investigated the therapeutic effects of pharmacological doses of vitamin C in a population of 44 pairs of school aged monozygotic twins ranging from 6 to 15 years. One member of each twin pair was randomly assigned to either the treatment group with either 500 mg, 750 mg, or 1000 mg of vitamin C, or the control group. Both twins were also given a daily multivitamin capsule containing 50 mg of ascorbic acid. During the 5-month study, the occurrence and severity of upper respiratory symptoms were monitored by a detailed symptom diary kept by the mother.

Treatment compliance was monitored by the retrospective assay of vitamin C excretion in urine samples collected at 1-month intervals. The results of this study showed no significant overall effect of pharmacological doses of vitamin C on the incidence of upper respiratory infections, although there was some equivocal evidence for an effect on the severity of colds. Girls in the younger two groups and males in the youngest group showed greater differences in the duration and severity of cold symptoms, but not in the incidence of illness episodes. However, even in these groups the administration of vitamin C accounted for only about 15-20 percent of the reported variation in disease severity. An unexpected finding in this study was an apparent effect of vitamin C on linear growth. Treated twins of both sexes in the youngest two age groups grew more than their co-twins during the 5-month period of study, but the effect was significant only in the lowest dosage group of male twins.

In order to investigate the hypothesis that pharmacological doses of vitamin C might influence growth, another co-twin study provided either a placebo or a single dose of 1 gm of vitamin C for 1 year to 27 young male twin pairs ranging in age from 5 to 12 years. Data from this study showed no significant differences in the frequencies, duration, or severity of

colds and no differences in growth between the control and treated twin. The co-twin study design appears to provide a high level of compliance by the study participants.

Another nutrition study using twins investigated the dietary intake of adult monozygotic twins using either the dietary recall interview or 3-day dietary diaries. Male twins were generally found to be more similar in their intake of the major nutrient groups, when estimates were based on recall rather than the dietary diaries. Similar results were obtained with respect to female twins for calories and fat intake. Two possible explanations for this finding are: the increased similarity in dietary intake of co-twins could reflect the fact that the individuals questioned ate together during the time period recalled whereas they were requested to eat apart during the period detailed in the dietary diary. An alternative explanation could be that twins tend to remember with a similar degree of accuracy food eaten in the same manner. The results of the study suggest that members of male twin pairs are characterized by a greater degree of similarity in dietary intake patterns than are members of female twin pairs even though they reside in different homes and have their meals selected and prepared by genetically unrelated spouses. These data do provide clear evidence for variation among genotype in food consumption and therefore stress the potential of twin studies as a tool in elucidating the factors which influence nutrition and nutritional choices.

Studies of the families of twins including twin parents, their spouses and offspring provide an in-depth look at both the genetic and environmental effects on the individual. This research design allows a partitioning of genetic and environmental effects. Two unique aspects of this design are: 1) its ability to detect maternal effects by comparing the correlations between the half-sib offspring of male and female twins, and 2) the insight the method can give into the causes and consequences of nonrandom mating through an analysis of the correlations that exist between twins and their spouses. Using this model to consider body weight and the correlations between male and female twins and their spouses, a relatively high correlation appeared between the genetically unrelated spouses of the male twins. A variation in the marital preferences of male twins with respect to the somatotype of their spouses is apparent that is not expressed in the spouses of female twins. The observed correlations for virtually all of the relationships observed in the kinships of male twins are higher than those seen in the female kinships. Such a finding can only indicate the presence of a pervasive environmental similarity among the members of male kinship not found in the families of the female twins.

Dr. Nance concluded that by using an environmental model of twin families, one can look at the pattern of correlations that allow for differences in the environmental covariations of the male and female kinships, special environmental effects between the twins, and the maternal environmental influence on the offspring. Thus, observations on twins and families of twins can lead to new insights into the causes and consequences of variation in human nutrition.

- 2) "Measurements of Trace Components in Human Tissues: The National Bureau of Standards Pilot Specimen Bank Program" was presented by Dr. Sally Harrison, Center of Analytical Chemistry, National Bureau of Standards, at the November 19, 1981 NCC meeting. A summary of her presentation is given below.

Credible analytical data are the foundation upon which answers to chemically-related scientific questions must be based. For the trace analysis of biological samples, including trace elements, credible data are obtained only when careful attention is given to every aspect of the analytical process; i.e., sample preparation, storage, and the analysis.

The Pilot Specimen Bank program is a feasibility study in environmental specimen banking funded by the National Bureau of Standards (NBS) and the Environmental Protection Agency. It is designed to respond to the need in environmental science to provide valid, pollutant baseline data and a means of tracing the history of newly recognized pollutants.

Areas of research in this program to date include: sample collection protocols for human livers and marine mussels; cryogenic homogenization procedures for biological tissues; evaluation of long-term sample storage methods; analysis of 36 human livers for approximately 30 trace elements; analytical methodology development for the analysis of organochlorine pesticide residues and organomercury compounds in livers and mussels; and methods for the determination of ultratrace levels of elements. In the development of procedures for collection, storage, and analysis of the samples, special care has been taken to eliminate possible sources of sample contamination or degradation and to understand the relationship between the trace component content of the analytical test portion and the original specimen. Particle free and/or specially cleaned Teflon materials have been used extensively for sample collection, homogenization, and storage to eliminate sample contact surfaces as sources of contamination. A titanium knife is used for dissection rather than the conventional stainless steel scalpel which is high in chromium and nickel.

Trace element analysis of 36 liver specimens has been carried out with values determined by two totally independent analytical techniques, namely, atomic absorption spectrophotometry and instrumental neutron activation analysis. Of particular interest from this analysis was the small range of values found for selenium--only a factor of 1.8 between the lowest and highest values. In the case of chromium, only three values were reported, and the remaining samples were less than 0.03 to 0.05 ug/g.

Dr. Harrison concluded that this research can have significant impact in other scientific areas, especially nutrition, with the immediate application of sample collection and storage procedures, homogenization techniques, and analytical methods. The trace element data, when evaluated with the sample collection information and demographic data on the donors, may be useful in assessing baseline levels for essential trace elements. The NBS program offers facilities, equipment, and samples that are available for collaborative studies in related areas of nutrition research.

- 3) "Aging and Nutrition in Nonhuman Primates" was presented by Dr. Douglas M. Bowden, Professor, Psychiatry and Behavioral Sciences, Adjunct Professor, Pharmacology; Associate Director, Regional Primate Research Center, University of Washington, at the January 28, 1982 NCC meeting. A summary of his presentation is given below.

Much of the research on nutrition and aging considers whether nutritional needs change significantly beyond the middle decades of life and, if so, how these needs change and what specific nutrients are involved. The study of human aging in terms of the genetic and other environmental factors that influence morbidity and mortality is an important area of research. Nutrition and diet is certainly one of the most influential environmental factors to exert chronic influence on the aging organism. Nutrition interacts with biological aging to produce or accelerate a multitude of afflictions that have their greatest incidence in the elderly and are considered part of the pathology of aging.

The nonhuman primates, because of their close genetic relation to humans, is the animal species which serves as an adequate model for studying the problems of aging. A 5-year project, which establishes a Macaca Nemestrina colony for multidisciplinary research on the biology of aging, is investigating 72 pig tailed macaques in a study of how nutrition--specifically the U.S. diet with its high proportions of lipid, cholesterol, simple sugars and sodium--and normal biological aging processes may interact to produce the physiological and behavioral changes, and diseases found in the elderly. Periodic examinations will provide information on 48 standard biological and clinical characteristics and four measures of biological aging. The studies are designed to clarify the effects of biological aging and diet on carbohydrate and fat metabolism, psychological functions, pharmacodynamics, genetic assurance mechanisms, and several specific disease processes such as periodontal disease, preneoplastic mammary dysplasia, etc. At the end of the 5-year study, specimens will be examined to determine whether the findings have any particular relevance to human aging.

Dr. Bowden concluded that the establishment of the Nemestrina colony as a national resource at the University of Washington will certainly help to stimulate high quality as well as an increased quantity of gerontological research studies in a number of areas including nutrition.

- 4) "Vitamin C and Iron" was presented by Dr. Arthur W. Nienhuis, Chief Clinical Hematology Branch, NHLBI, at the March 25, 1982 NCC meeting. A summary of his presentation is given below.

Clinical observations of the Bantu in South Africa provided some of the first clues of ascorbic acid involvement in iron metabolism. Due to their practice of drinking beer brewed in iron pots, these tribesmen ingested approximately 100 mg of iron each day but remained immune to detrimental effects of iron overload. Despite a manyfold increase in the total body iron burden, the Bantu often had nearly normal serum levels of iron and transferrin saturations. Most of the excess iron was found in the reticuloendothelial cells, particularly in the spleen and liver, and also the pancreas. An interesting finding was that

scurvy and a form of osteoporosis due to ascorbic acid deficiency were found to be associated with the iron overload in this population. The clinical ascorbic acid deficiency was thought to be attributable to the accelerated oxidative metabolism of ascorbic acid as a result of excess iron and low dietary intake of vitamin C. Repletion with vitamin C was often accompanied by a rise in serum iron.

Studies have also shown that patients with severe B-thalassemia, who receive regular blood transfusions, develop secondary hemochromatosis and often have low serum and white cell levels of ascorbic acid. A subclinical ascorbic acid deficiency is common, and administration of ascorbic acid has very definite and quantifiable effects on iron metabolism.

Data have revealed that the administration of ascorbic acid may be harmful in the presence of iron overload. In studies on the effect of ascorbic acid (500 mg/day) on iron absorption in thalassemia patients treated with intramuscular deferoxamine, it appears that many patients experienced striking, often transient, deterioration in left ventricular function. In animal studies, treatment for ascorbic acid deficiency in guinea pigs has resulted in the mobilization of iron from the spleen and deposition in the liver. Also, the peroxidative effect of iron on lipid membranes is shown to be enhanced with ascorbic acid. Therefore, it seems plausible that the administration of ascorbic acid to thalassemia patients would lead to increased damage to cells already heavily laden with iron, and also lead to a redistribution of iron from the reticulo-endothelial cells to parenchymal cells.

A recent study report of a patient with thalassemia who had an iron overload from multiple transfusions revealed the presence of scurvy and poor bone healing. Treatment with vitamin C increased serum iron, serum ferritin, and iron excretion in response to deferoxamine. The iron deposition may have been predominately in the reticuloendothelial cells, held there by virtue of the deficiency in vitamin C, and then released into the serum when ascorbic acid was given. This data support the idea that ascorbic acid deficiency may be beneficial to the patient with iron overload.

Dr. Nienhuis concluded that the effects of vitamin C are potentially important only in the presence of iron overload. Clearly, patients with advanced primary or secondary hemochromatosis, particularly those with overt cardiac disease, should reduce their intake of vitamin C to a minimum. In general, a moderate reduction of vitamin C may be beneficial at the beginning of a transfusion program. Also, in patients treated with deferoxamine, the need for vitamin C should be documented by measurements of iron excretion before and after supplementation. Deferoxamine, which binds iron, can block the potentially harmful peroxidation of membrane lipids that vitamin C is known to enhance. Clinical studies are needed to examine the results of ascorbic acid administration in patients treated with deferoxamine.

- 5) "Dietary Carbohydrate, Food Intake and Growth of Infants" was presented by Dr. Sam Fomon, Professor, Department of Pediatrics, University of Iowa Hospitals and Clinics, at the May 27, 1982 NCC meeting. A summary of his presentation is given below.

Studies on infant feeding have shown that infants prefer sweeter formula feedings during the first few days of life (i.e. sucrose over lactose and fructose over glucose). A study of normal female infants from 8 to 112 days of age found that infants fed the sucrose containing formula had greater mean energy intake per unit of body weight and greater mean gains in weight than those infants fed polyose (a cornstarch hydrolysate of bland taste).

Results from this study suggest that differences in the type of carbohydrate in an infant formula influence food consumption; however, with longer term feeding (> 20 to 28 days), adaptation to the formula might occur in that the infant may adjust formula consumption to meet energy needs independent of the type of carbohydrate in the formula.

Dr. Fomon concluded that the possibility that differences in sweetness may lead to differences in weight gain and/or body composition require careful research assessment. Although this study attributes the greater energy intake with sucrose as a result of its greater sweetness, other possible mechanisms include an alteration in insulin secretion with sucrose or stimulation of the sympathetic nervous system activity with sucrose. The mechanisms by which the kind of carbohydrate influences food consumption remain to be defined.

- 6) "Mechanisms of Food Hypersensitivity" was presented by Dr. Dean Metcalfe, Senior Clinical Investigator, Allergic Diseases Section, Laboratory of Clinical Investigation, NIAID, at the June 24, 1982 NCC meeting. A summary of his presentation is given below.

Although complaints of food allergy approach 25 percent, the true incidence is probably much less, e.g. the incidence among children has been estimated at 0.3 percent and may decrease with age. Immunologically mediated reactions to foods are expressed clinically by a diversity of signs and symptoms ranging from abdominal pain to generalized anaphylaxis. The clinical expressions of food allergy are influenced by factors including the age and awareness of the patient, the quality and quantity of the food ingested, and the type and extent of associated medical problems.

Food allergies can be expressed in the gastrointestinal system resulting in nausea, vomiting, cramping, pain, flatulence, and diarrhea, as well as in the skin. Asthma and rhinitis are common in children, while neurological problems such as behavioral disturbances and depression as manifestations of central nervous system involvement in food allergy remain to be conclusively demonstrated. Systemic anaphylaxis resulting from an allergy to ingested foods can occur within minutes or as late as hours after ingestion of the offending food.

The majority of allergic reactions to food appear to be based on the Type I immediate hypersensitivity mechanisms which occur in the gastrointestinal tract, where the IgE coated mast cells are first involved. The presence of IgE on the mast cell surface has been demonstrated by immediate reactions following injection of minute amounts of food antigens into the skin; human mucosal mast cells have been reported to degranulate in

vitro in an IgE dependent reaction. Mast cell degranulation results in the release of mediators of allergic reactions (i.e., histamine, chemotactic factors, heparin release bring on local changes in blood vessels, mucous production, muscle contraction, inflammation, etc.). Research in this area has also demonstrated that Type III antigen-antibody mechanisms are involved in food allergies. IgA, IgM, and IgD directed against specific food determinants have been shown in gastrointestinal secretions and in serum. Complement activation within the bowel wall may also be involved and lead to mast cell degranulation, thereby giving the Type III reaction the clinical resemblance of a Type I reaction. Observations also suggest a Type IV, delayed hypersensitivity reaction to oral ingestants; a Type II, cytotoxic hypersensitivity, has not been shown.

The diagnostic techniques used for determining food allergies include: 1) a medical history; 2) elimination diets; 3) test responses to food extracts; and 4) oral challenge. A medical history, including a detailed account of specific reactions to foods, is helpful in identifying the suspected food antigen (usually glycoprotein with a molecular weight between 18,000 and 16,000 daltons). A suspected food may fail to consistently lead to an allergic reaction due to the amount consumed, presence of other simultaneously ingested foods that may delay digestion, the state of the food, and the possibility that medications such as antihistamines may have altered the reactions. Foods may also be contaminated by substances such as mold, dyes, additives and bacteria that lead to reactions and these are confused with food allergy. In addition, intrinsic properties of certain foods lead to problems resembling food allergy. Prunes, soybeans, and onions can cause gastrointestinal problems by themselves without the involvement of allergic manifestations. Caffeine consumed in large amounts causes nervousness, tremor, and tachycardia in some people. A medical history will help to identify any gastrointestinal disturbances resulting after food ingestion.

Elimination diets are used clinically to remove an offending food from the diet of the affected individual so as to resolve the food induced illness. If symptoms are resolved on the restricted diet, resumption of a normal diet should be accompanied by a return of symptoms.

Both in vivo and in vitro diagnostic procedures can be used to support the diagnosis of food allergy. Skin testing with dilute water soluble food extracts is accomplished using scratch or puncture techniques. This test will bring on a local wheal and flare reaction typical of Type I hypersensitivity in those individuals with IgE antibody to the food antigen.

Additional diagnostic tests for food allergies include the radioallergen sorbent test (RAST) used to demonstrate the presence of serum IgE to a specific antigen, the basophil histamine release test with degranulation to dilute suspensions of food antigens, and the provocative sublingual test which uses food extracts to diagnose food sensitivity.

The basic procedure for the diagnosis of food intolerances is the oral food challenge. A single unequivocal positive reaction such as hives or asthma to a food tested may be taken as reasonable evidence of a adverse reaction to food.

Dr. Metcalfe concluded that research results have shown that the only specific treatment of food allergy is avoidance. In severe cases it may be necessary to use adrenalin, while less severe symptoms can be controlled by antihistamine and anticholinergic drugs.

7) "National Caries Program, NIDR" was presented by Dr. James P. Carlos, Director, National Caries Program, NIDR, at the July 22, 1982 NCC meeting. A summary of his presentation is given below.

Nutrition is a high priority of the National Caries Program (NCP) since the presence of monosaccharides and disaccharides (fermentable sugar) in the oral cavity has long been associated with the development of dental caries. As a result of public education on the relationship of frequent ingestion of sugar to caries development, 30 percent of households have attempted to lessen their sugar intake by dietary restrictions, or by substituting artificial sweeteners. Despite this intent, total per capita consumption of fermentable sugar used as sweeteners in the United States continues to increase due largely to the increase in the use of corn-derived sweeteners (glucose and fructose). Even though the consumption of sucrose (cane and beet sugar) has continued to decrease, the consumption of corn-derived sweeteners has more than offset the decrease in sucrose consumption.

Accompanying the increased per capita consumption of sugar sweeteners in the last 10 years has been a 40 percent increased per capita consumption of the sweetener saccharin, whose status is in limbo due to the congressional moratorium on the 1977 FDA ban on saccharin use.

The NCP has supported a number of research grants and contracts to develop a variety of noncariogenic sweeteners. NIDR investigators have synthesized several intensely sweet dipeptide esters which show more stability than the recently approved aspartate sweetener. In recent years, plant-derived sweeteners used by native populations in other countries have shown promise for use in the U.S. Scientists have isolated, purified, characterized and subjected to a taste panel all the sweet principles from Stevia rebaudiana, a plant native to Paraguay. Extracts from this plant are used in Japan in commercially produced foods such as chewing gum, soft drinks, sauces, and pickles. Other alternate sweeteners, used by native populations, are under study from the following plants: Hydrangea thumbergii, native to Japan; Mormodica grosvenori, native to southern China; and Lippia dulcis, native to Mexico. In order to test for potential health hazards of the sweeteners, long-term chronic toxicity testing, acute toxicity testing, mutagenicity testing, and taste testing must be conducted with more than one animal model.

In addition to sugar, other factors known to modulate the cariogenicity of foods include eating frequency, presence of cariostatic agents, food texture, food stickiness, and induction of salivation. To examine these factors, NCP scientists have developed a highly reproducible rat model that provides enterally essential nutrition, as well as 17 daily snack foods at hourly intervals. The cariogenic potential index (CPI) of a food is determined by the ratio of the caries scores resulting from the

ingestion of the test food compared to powdered sucrose. The CPI of foods tends to increase with increasing sugar content, as in the case of breakfast cereals. However, some results indicate that the elements in foods which give rise to an increased CPI are not fully understood. This rat model shows great promise in examining the complex relationship of those factors important to the cariogenicity of a particular food. Because the test food is the only food that comes into contact with the rat's oral cavity, the rat model can be used to measure the relationship of a food's CPI value and other parameters, such as the salivary enzyme activities and the presence or absence of immune factors.

For the first time, a longitudinal prospective study is under way on the relationship between dietary intake patterns and the development of dental caries in a general population of school age children residing in a nonfluoridated area. Multiple short-term, dietary intake measurements of total daily sugar consumption; total daily calories in terms of protein, fat, and carbohydrate; and total daily frequency of eating or drinking will be collected from 800 school children, ages 11 to 13 years. This study will correlate new oral lesions with the kind of food intake as well as the frequency of food intake.

Dr. Carlos concluded that the NCP program involves simultaneous research and development efforts to attenuate each of the factors in the etiology of caries: specific oral mechanisms, a susceptible tooth, and a diet rich in sugars. In addition, the NCP is involved in efforts to improve the delivery and public utilization of caries preventive measures.

- 8) "MRFIT--Risk Factor Changes and Mortality Results" was presented by Dr. Jeffrey Cutler, Scientific Project Officer, Clinical Trials Branch, NHLBI, at the September 30, 1982 NCC meeting. A summary of his presentation is given below.

The Multiple Risk Factor Intervention Trial (MRFIT) was a randomized primary prevention trial to ascertain whether a special multifactorial intervention program for changing risk factors in 12,866 men between 35 to 57 years of age, at increased risk of death from coronary heart disease (CHD), can result in a significant reduction in mortality of CHD. Beginning in 1973, the men were accepted in the trial based on the presence of one or more of the major risk factors associated with CHD; i.e., elevated serum cholesterol, elevated diastolic blood pressure, and cigarette smoking. The men were determined to be clinically free of CHD and sufficiently motivated to participate in a 6-year program before being randomly assigned either to a special intervention (SI) program consisting of stepped-care treatment for hypertension, counseling for cigarette smoking, and dietary advice for lowering blood cholesterol levels, or to their usual source of health care in the community (UC).

A necessary intermediate goal of the trial was to obtain adequate reductions through intervention of the three risk factors; highly statistically significant differences for each of the risk factors were observed between the SI and UC groups. In addition, risk factor changes were also observed in the UC group, though to a lesser degree. For example, over 6 years, smoking declined from 59 percent to 46 percent, diastolic blood pressure

declined from a baseline value of 90.9 to 83.6 mmHg, and plasma cholesterol levels from 241 to 233 mg/dl. Also, 47 percent of the UC men were receiving antihypertensive medication at the end of the sixth year compared with 19 percent at baseline. The cause of these unanticipated changes in the UC group is speculative.

The following four key endpoints were identified for MRFIT: death from CHD (the primary endpoint); death from cardiovascular disease (CVD); death from any cause; and the combination of fatal CHD and nonfatal myocardial infarction. Deaths ascribed to CHD were subclassified as (1) myocardial infarction with death occurring within 30 days of onset of symptoms or during hospitalization for acute myocardial infarction; (2) sudden death within 24 hours of symptom onset and without documented myocardial infarction; (3) congestive heart failure due to CHD; or (4) death during hospitalization for surgery for CHD or from complications of such an operation.

After a 7-year followup, 260 deaths occurred among UC men, 124 were ascribed to CHD and 145 to cardiovascular causes (including CHD). Of the 265 SI deaths, 115 were ascribed to CHD and 138 to CVD.

The key mortality endpoints of CHD and CVD were 7.1 percent and 4.7 percent less, respectively, in the SI compared with the UC group, while the death rate for all causes was 2.1 percent higher for the SI men. The number of deaths from noncardiovascular causes was also similar in the two groups (116 SI vs. 109 UC); 81 cancer deaths occurred in the SI and 69 in the UC, resulting from lung cancer (34 SI vs. 28 UC), colorectal cancer (8 SI vs. 6 UC), other gastrointestinal neoplasms (20 SI vs. 11 UC) and other neoplasia (19 SI vs. 24 UC). The 260 deaths in the UC group was substantially short of expectation, based on design risk factor change assumptions and Framingham risk functions.

The lower than expected UC mortality could have resulted from: 1) the recent reduction in CHD mortality in the U.S., 2) exclusion criteria applied to the MRFIT screened group resulting in the selection of men with a lower than expected mortality in both the SI and UC groups, 3) the phenomenon of lower than expected mortality in almost all clinical trials involving volunteers, and 4) the substantial risk factor changes made by the UC men.

Possible explanations for the overall mortality results observed in the trial are (1) that such an intervention program is without benefit in terms of substantial decreases in mortality; (2) the hypothesis received a less than definitive test, and the observed differences in mortality represent chance deviations from a larger effect than this intervention program has in its population; and (3) one or more constituents in the intervention program may have had an unfavorable effect on survival in some subgroups offsetting the beneficial effects of others. The last explanation for the difference in the mortality results seems most plausible.

Dr. Cutler summarized his presentation indicating that it is possible to change coronary risk factors with considerable success through an

intensive long-term intervention program such as MRFIT. The overall results, however, do not show a beneficial effect on CHD or total mortality from this multifactor intervention. The unexpected declines in risk factor levels and the lower than expected mortality in the U.C. group could have accounted in part for a less than optimal test of the multifactor intervention. The SI-UC comparisons indicate that among men with normal baseline ECGs, the MRFIT intervention program may have had a favorable effect on CHD mortality. The data also suggest that men with hypertension, primarily those with resting ECG abnormalities, had no favorable, and possibly an unfavorable, response to intervention. More study is required to clarify this issue and its possible relation to antihypertensive treatment. Findings also include the within-group observation that men who stopped cigarette smoking had lower CHD and total mortality than those who continued to smoke.

The Videotape Series, "EAT WELL, BE WELL II"

In FY 1981, the Metropolitan Life Insurance Company asked the NCC to serve as consultants to the production of a series of videotapes on various nutrition topics entitled "Eat Well, Be Well." This series was produced by Amram Nowak Associates with funds from the Metropolitan Life Insurance Company. This first series was an excellent example of successful joint industry and government cooperation in a nutrition education endeavor.* Following the wide public and professional acceptance of the first "Eat Well, Be Well" series, the NCC agreed to serve as consultants in a second production, "Eat Well, Be Well II."

"Eat Well, Be Well II" is even more exciting since it involves the successful collaboration among industry, Government and the scientific community in promoting public health. Its theme song emphasizes the role of proper nutrition and exercise in maintaining health, which is consistent with Mr. Schweiker's (the former DHHS Secretary) interest in health promotion. This second "Eat Well, Be Well" series consists of 14 7-minute videotape segments that explain the role of nutrition in health promotion and disease prevention. In fact, nine segments feature prominent physicians explaining the role of nutrition in health and disease. One segment features Secretary Richard S. Schweiker, explaining the importance of a regular exercise routine to health promotion. Another segment on "Body Weight" features Dr. Artemis P. Simopoulos, the NCC Chairman and Dr. Paul Entmacher, the Vice President and Chief Medical Director of the Metropolitan Life Insurance Company. The series also includes a segment by a farmer from Illinois speaking on the production of low-fat meat, and an ethnic program with people of various backgrounds displaying the foods they commonly eat. Helen Hatton, home economist and chef in the "Eat Well, Be Well" series is again featured demonstrating appropriate recipes for the various nutrition topics.

A brief summary of each of the 14 segments is presented below, along with the title of the featured recipe and commentator.

*The first "Eat Well, Be Well" series was described in detail in the FY 1981 Annual Report of the NIH Nutrition Program on pages 103-104.

Segment #1 - Milk and Dairy Products

Dr. Lawrence Riggs, Mayo Clinic, Rochester, MN, discusses the importance of dairy products at all ages for bone growth, strength and size; the meaning of osteoporosis, its prevention and detection. The recipe featured, "Better Blintz," uses low-fat cottage cheese and buttermilk to make the dish more easily digestible.

Segment #2 - Dieting

Dr. Theodore Van Itallie, Director, Obesity Research Center, St. Luke's Hospital, NY, discusses the meaning of obesity, its relationship to diet and the effects of sensory specific satiety as demonstrated through the use of animal models. The recipe, "Ginger Pork," features a one-dish meal prepared the stir-fried way that may help to keep food intake down.

Segment #3 - Protein

Mr. Denny Dolmach, a cattle farmer from Grundy Center in Illinois, discusses the grading of meat as it relates to fat content. A visit to his family cattle farm shows feeding methods appropriate for the production of tasty beef containing less fat. The recipe "London Broil Pomadora," features a high protein dish made from a lean, less expensive cut of meat.

Segment #4 - Ideal Body Weight

Dr. Artemis P. Simopoulos, Chairman, NIH Nutrition Coordinating Committee, and Dr. Paul S. Entmacher, Vice President and Chief Medical Director, Metropolitan Life Insurance Co., discuss ideal (desirable) weight and the difference between "average" and "ideal" weight, with references to the 1959 and 1979 studies done by Metropolitan. The importance of maintaining weight through exercise, and variety and moderation in eating are also discussed, and tips on meal planning are given. The recipe, "Lucky Seven Tuna," features a well balanced, low calorie meal that can be prepared one day and eaten the next.

Segment #5 - Carbohydrates

Helen Hatton discusses the benefits and misconceptions about eating carbohydrates such as pasta, potatoes, and grains. A visit to a pasta factory includes a demonstration of pasta being cut. The recipe, "Spinach Lasagna Verde," offers a pasta dish made with spinach lasagna.

Segment #6 - Vitamins and Minerals

Dr. Victor Herbert, Chief, the Hematology and Nutrition Lab., Bronx Veterans Medical Center, and Past President, American Society of Clinical Nutrition, discusses the U.S. Recommended Dietary Allowances (RDA's), the importance of a well balanced diet containing foods from the four food groups, and fast foods in variety and moderation; and vitamin and mineral pills. The recipe, "Chicken Couscous," features a dish which supplies a high percent of the RDA's and is filled with vitamins and minerals.

Segment #7 - Alcohol

Dr. Charles Lieber, Director, Alcohol Research Unit, Veterans Administration Hospital, NY, discusses the effects of alcohol on the liver and the lack of nutrients (empty calories). He discusses research on alcohol consumption of primates that proved that alcohol, even in the absence of a dietary deficiency, can injure the liver as well as other tissues of the body. The use of alcohol in cooking for tenderizing and enhancing the flavor of foods is discussed. The recipe featured, "Scallops on a Skewer," is a seafood dish perked up with a little alcohol.

Segment #8 - Cholesterol

Dr. Virgil Brown, Mt. Sinai School of Medicine, NY, discusses the importance of knowing the blood cholesterol level and the amount of cholesterol carried in high density and low density lipoproteins in order to determine the need to limit saturated fat intake. He discusses the lipoprotein system and the function of HDL's and LDL's through the use of an analogy--the flow of traffic through a tunnel. The recipe, "Snappy Snapper," features a cold poached snapper salad with a basil lime vinaigrette.

Segment #9 - Vegetarianism

Dr. Albert Mendeloff, Professor of Medicine, Johns Hopkins University, MD, and Editor, American Journal of Clinical Nutrition, discusses the meaning of vegetarianism, and the problems as well as the advantages of the vegetarian diet. One section shows a visit to the Seventh Day Adventist College in Takoma Park, MD, where vegetarianism is practiced. The recipe, "Garden Curry," is a vegetable curry dish.

Segment #10 - Fiber

Dr. Albert Mendeloff, one of the leading researchers in the field of fiber, discusses the meaning of dietary fiber in terms of what it is and and its benefits. "Cracked Wheat Long Johns," the recipe featured, is a dish which will add to dietary fiber intake.

Segment #11 - Food Substitutions

Helen Hatton discusses foods or ingredients that are nutritionally wiser, such as fresh and dry herbs and spices instead of salt, yogurt in place of sour cream, and margarine instead of butter. The recipe featured is "Squash with Bean Balls."

Segment #12 - Prenatal Diet

Dr. Roy Pitkin, Professor of Obstetrics and Gynecology, University Hospital, IA, discusses the importance of a well balanced, well rounded prenatal diet and the need for additional nutrient intake in terms of calories and other nutrients such as calcium during pregnancy. The recipe, "Strawberry Rice Parfait, is a delicious dessert that is made with milk and provides some of the needed calcium.

Segment #13 - Ethnic

Helen Hatton discusses Mexican, Spanish, Chinese and Middle Eastern foods in this grocery store eat-well-ethnic travelogue. The recipe features a Middle Eastern dish, "The Real Tabouli," made primarily from cracked wheat and parsley, which is eaten as a salad or a side dish.

Segment #14 - Diet and Exercise

Richard S. Schweiker, Secretary, Department of Health and Human Services, discusses health promotion and the concept of "wellness," as well as the importance of a regular exercise program. A section on running features Secretary Schweiker with Helen Hatton.

The "Eat Well, Be Well II" series will be beamed by satellite to all the Public Broadcasting System television stations in July 1983. This series could be used for nutrition instruction in primary and secondary schools, by church groups, as part of health fairs, and by any group interested in the role of nutrition in health and disease as well as the very important role of the combination of exercise and diet in maintaining health.

Conferences Sponsored by the NCC

The NCC mandate calls upon the NCC to sponsor conferences, workshops, and symposia in areas of nutrition research that are of concern to the Institutes. In FY 1982, the NCC and the Centers for Disease Control sponsored the "Workshop on Body Weight, Health and Longevity." This workshop was held in Bethesda, Md., January 25-26, 1982, under the aegis of the DHHS Nutrition Research Initiative. A description of the workshop and its conclusions are presented along with the DHHS Nutrition Research Initiative on pages 147-9 of this report.

SUBCOMMITTEE ON NUTRITION EDUCATION ACTIVITIES AND ACCOMPLISHMENTS

The charge of the Subcommittee on Nutrition Education is:

- ° To review NIH nutrition publications designed for the public
- ° To develop public service announcements
- ° Develop and implement National Nutrition Month activities at NIH.

In FY 1982, in accordance with its charge, the Subcommittee on Nutrition Education reviewed various Institutes' nutrition publications intended for the public, developed a comprehensive program of nutrition activities to be carried out at the NIH during National Nutrition Month, March 1982, and initiated the development of the NIH-NCC Nutrition Research Exhibit.

In addition, the subcommittee continues to work with the GSI Cafeteria Service, through the NIH Area Manager, to introduce more nutritious food

selections as part of the regular NIH cafeteria service. Listing the calorie content of certain foods regularly available in the NIH cafeteria is a new service of the GSI Cafeteria Service to provide nutrition information to employees.

The subcommittee expects to publish the pamphlet "Snacks and Your Health, Dietary Guidelines for Americans," that denotes those snacks considered appropriate by all the NIH Institutes. In order to avoid duplication of effort and enhance the quality of the nutrition education materials destined for the public, the subcommittee plans to work closely with the nutrition education staff of the CNRU's. The subcommittee will serve also as a focal point for providing the CNRU Directors and staff with information on nutrition materials and resources available from the NIH and other agencies within the DHHS.

National Nutrition Month at the NIH, March 1982

In March 1982, a variety of activities emphasizing the importance of sound nutrition and adequate exercise were held at the NIH to commemorate National Nutrition Month, as designated by the American Dietetic Association. The NCC and the Subcommittee on Nutrition Education cosponsored these activities with the cooperation of the Recreation and Welfare Association (R&W), the Occupational Medical Service (OMS), and the GSI Cafeteria Service.

The theme for the program "MARCH FOR GOOD NUTRITION: Take Steps Against Disease," featured on posters on the bulletin boards and in the cafeterias, as well as on tent cards, emphasized the importance of sound nutrition habits to help prevent such afflictions as heart disease, obesity, high blood pressure, cancer, dental caries and others. This poster was also featured during the month by all GSI operated cafeterias in the Washington, D.C. metropolitan area.

The kickoff to a series of major events scheduled for the month was a special program on "The History of the Science of Nutrition at the NIH." The program featured Dr. W. Henry Sebrell, NIH Director from 1950 to 1955, who presented an enlightening historical perspective on the beginnings of nutrition research at the NIH, particularly in the area of pellagra, a vitamin B₁ deficiency state. Dr. Sebrell indicated that during his time at the NIH, with the advances being made in enzymology, the scientific base of nutrition research began to expand. Dr. Artemis P. Simopoulos, the NCC Chairman then described the development and direction of nutrition research at NIH from 1955 to the present. Upon completion of the program, the audience was invited to view the exhibit on "The History of Nutrition" featured at the Clinical Center's library, which was displayed during the entire month.

Two R&W programs emphasizing the theme of "Fitness as a Lifestyle for You and Your Family," included a demonstration of morning wake-up and desk exercises, especially those important for strengthening the lower back and reducing or eliminating muscle contraction or fatigue during periods of stress; a demonstration by the NIH Judo Club; aerobic dances; a talk by a member of the YMCA on the importance of a regular exercise

routine; and a film from The President's Council on Physical Fitness and Sports on the importance of fitness in our everyday life. The benefits from the different forms of exercise that could be practiced by various family members were emphasized.

Another scheduled event on exercise, "The Family Run: Golden Carrot Day," included various sprints and running events appropriate for children, adolescents and adults. Members of Health's Angels, the NIH jogging club, assisted in establishing the appropriate courses.

Two brown bag luncheons--one sponsored by DRR entitled "Nutrition and Well-Being" and one by NIDR--provided NIH personnel with an opportunity to get answers from professional nutritionists to many nutrition questions such as: "What is the role of vitamins in prevention of disease?" and "What are empty calories?"

The OMS sponsored a nutrition education workshop on four consecutive Tuesdays to cover the topics of food value, behavior modification, psychological aspects of overeating, and the pros and cons of popular diets.

The GSI Cafeteria Service offered a number of new nutritious food selections as well as nutrition information on certain food items. The specials featured included the "Lean Lunch and Breakfast Bunch"; salt-free vegetables; the "Nutrition Month Salad Bar," complete with calories listed for approximately 15 toppings; and a health food promotional program with natural drinks, cookies, snacks and fanciful fruits.

Other scheduled events included viewing of films and videotapes on nutrition such as segments from "Eat Well, Be Well I," the "Sugar Film," and "Super Jock."

In addition to the scheduled activities, the Subcommittee on Nutrition Education conducted a nutrition education intervention pilot project on the transfer of nutrition information at the workplace. The objective of the project was to make the NIH employees aware that information and consultative resources about nutrition are easily available upon request. The project consisted of a pretest survey, an intervention and a post-test survey. The intervention component of the project consisted of distributing and collecting the "NIH Nutrition Information Sheet" which listed the nutrition publications available to the public from the NIH, as well as other government agencies, professional societies and consumer groups. Results of this study will be available in FY 1983.

NIH-NCC Nutrition Research Exhibit

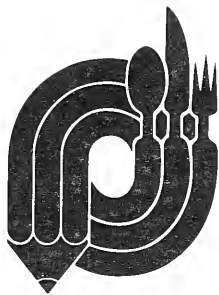
In May 1982, a proposal to develop the NIH-NCC Nutrition Research Exhibit was brought before the NCC by the Subcommittee on Nutrition Education. The rationale behind this exhibit was to provide the scientific community, health professionals, interested consumers, and the general public with information regarding the NIH Program in Biomedical and Behavioral Nutrition Research and Training at the site of various scientific meetings. The exhibit proposed is to depict the nutrition research program activities

of the Institutes and Divisions; be suitable for travel; be staffed by persons capable of providing general information on the NIH nutrition program as well as referring specific questions to appropriate staff within the Institutes; and be designed to serve both multidisciplinary as well as regional or national meetings focused on specific areas of science. The proposed idea for a nutrition research exhibit was accepted by the NCC as a worthwhile activity of the subcommittee.

The theme selected for the exhibit illustrates the transfer of nutrition research from basic laboratory studies to clinical research that ultimately serves to educate persons on the role of nutrition in health promotion, disease prevention, and disease treatment. The exhibit will consist of various panels representing a categorical display of nutrition research as it relates to growth and development, to health promotion throughout the various stages of the life cycle, and to the prevention and treatment of diseases such as cancer, coronary heart disease, hypertension, obesity, dental caries, etc.

A pamphlet entitled "Nutrition Research at the National Institutes of Health" is being prepared to accompany the exhibit and to provide descriptive information on the overall NIH nutrition program, as well as information on the application and review process for grants, projects, etc., and names of contact persons for the nutrition program within each Institute.

It is hoped that the NIH-NCC Nutrition Research Exhibit, with the accompanying pamphlet, will serve to illustrate the NIH commitment to nutrition research, stimulate nutrition research along the lines of individual Institute's program interests, and encourage high quality applications for research projects in basic research, clinical investigation and in the epidemiological aspects of nutrition science.



III.

NUTRITION COORDINATING COMMITTEE OFFICE

The Nutrition Coordinating Committee office staff represents the NIH on a number of nutrition related committees involving other Federal agencies and departments, and the Office of Science and Technology Policy (OSTP) in the Executive Office of the President. In addition, the staff is primarily responsible for responding to information requests about nutrition in general and about the NIH nutrition program in particular.

ACTIVITIES OF THE NCC OFFICE

As in past years, in addition to staffing the NCC and its subcommittee, the NCC office responded to a great number and variety of requests for information on nutrition and the NIH nutrition program from the Congress, other Federal agencies, the scientific community, and the public. The major responsibilities of the NCC office were: to compile and analyze the data on the NIH nutrition program in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, "The Justification of Appropriations Estimates for Committee Appropriations" (Moyer Material on the NIH Nutrition Program), and the "Trans-NIH Nutrition Research Program" section of the report on NIH Extramural Programs; to collect and analyze data in preparing testimony and "special presentations" for the Office of the Director, NIH, and the Office of the Assistant Secretary for Health, DHHS; to present the NIH nutrition program at national conferences and at meetings of professional societies; to assist the NIH Information Office with the preparation of press releases; and to provide input into DHHS nutrition activities.

The NCC Chairman serves as initiative coordinator of the Departmental Research Initiative in Nutrition. The NCC Chairman also cochairs and serves as the Executive Secretary of the Joint Subcommittee on Human Nutrition Research in the Office of Science and Technology Policy. The JSHNR was established September 28, 1978, as evidence of the increased interest in nutrition research in the Executive Office of the President, the White House.

The NCC office has responded to information requests on nutrition, nutrition research, and the NIH Program in Biomedical and Behavioral Nutrition Research and Training from a broad spectrum of sources: the Congress, the Office of Technology Assessment, and the General Accounting Office; the Executive Branch, including the Office of Science and Technology Policy, the Office of Management and Budget, and various agencies of the Public Health Service; as well as from the scientific community and the public. The central focus provided by the office has undoubtedly facilitated NIH responses.

In order to expeditiously develop reports on each Institute's nutrition program and on the overall NIH Program in Biomedical and Behavioral Nutrition Research and Training, the NCC office maintains a computerized system for data retrieval on all nutrition research and training activities in the extramural and intramural programs at the NIH. This computerized data retrieval system was utilized to develop the tables and figures for this report as well as to respond to queries from Congress, the scientific community, and the public on an ad hoc basis.

Congressional Hearings on Nutrition

In FY 1982, the NCC office staff provided input to the following hearing:

The hearing on "Federal Commitment to Human Nutrition Research" was held on June 23, 1982, before the Subcommittee on Science, Research and Technology of the House Science and Technology Committee, and the Subcommittee

on Department Operations, Research and Foreign Agriculture of the House Agriculture Committee. The purpose of the hearing was to ascertain the Federal government's commitment to human nutrition research, including the implementation plan for the National Nutrition Monitoring System (NNMS) that was submitted jointly to Congress by the DHHS and USDA. The Assistant Secretary for Health, DHHS, testified on the nutrition research expenditures for DHHS in FY 1981 and specific nutrition research activities conducted by NIH, NCHS, FDA and CDC. He noted that significant progress has been made over the last year in implementing the NNMS and in coordinating nutrition efforts with USDA; e.g., the coordinating and integration of the National Health and Nutrition Examination Survey (NHANES) of NCHS and the USDA National Food Consumption Survey. The Assistant Secretary also stated that the DHHS plans to review the report "Diet, Nutrition and Cancer" published by the National Academy of Sciences, National Research Council, pointing out that the recommendations given in the report are merely interim guidelines since more research is needed to fill in the knowledge gaps of the role of nutrition in cancer promotion and prevention. The NCC Chairman accompanied the Assistant Secretary for Health at the hearing and responded to questions.

Official Reports and Special Presentations on Nutrition

The NCC Office has provided information on the NIH or DHHS nutrition research activities for inclusion in reports prepared by the General Accounting Office (GAO), as well as by other Federal agencies such as USDA. In addition to numerous special reports the NCC office annually supplies data used in the preparation of the following documents:

"The Justification of Appropriation Estimates for Committee on Appropriations" (Moyer material on the NIH Nutrition Program), prepared by the NCC Office and the NIH Office of Communications at the request of the Labor-DHHS Appropriations Subcommittee of the House of Representatives, includes the financial obligations in nutrition of the PHS (NIH, FDA, CDC, HRA, ADAMHA) and the Office of Human Development, Administration on Aging, along with a description of each agency's nutrition program.

"The Program in Biomedical and Behavioral Nutrition Research and Research Training" section of the report on NIH Extramural Programs, which is a compendium of descriptions of all scientific programs supported by the B/I/D's. In addition to the nutrition program other trans-NIH programs described in the report include diabetes, arthritis, and digestive diseases.

Throughout the year, the NCC Chairman and office staff presented the NIH nutrition program and made special presentations on nutrition at the invitation of professional societies and other national and international groups interested in nutrition. In FY 1982 over 12 such presentations were made before national and international organizations such as the American Health Foundation, American Heart Association, American Medical Association, the President's Council on Physical Fitness and Sports, and the National Nutrition Consortium.

Each year the National Nutrition Consortium sponsors the Nutrition Policy Seminar for graduate students from various universities across the country. Formal presentations and informal panel discussions are conducted by representatives of all facets of the food and nutrition public policy community, including relevant congressional committees, regulatory agencies, research agencies, scientific organizations, and industry and consumer groups. The NCC Chairman presented the NIH nutrition program at the 1982 seminar.

The NCC Chairman chaired the session on "Macronutrients and Blood Pressure" at the Conference on Nutrition and Blood Pressure Control: Current Status of Dietary Factors and Hypertension, held September 13-15, 1982, and cosponsored by the International Life Sciences Institute, DHHS, and the National Kidney Foundation. The proceedings of the conference were published in the Annals of Internal Medicine, May 1983, volume 98, #5 (part 2). Another conference in which the NCC office actively participated was the "Nutritional Therapy in Chronic Renal Failure Conference," held April 29-30, 1982, and sponsored by the NIADDK. The NCC Chairman chaired the panel on "Nutritional Aspects of a Clinical Trial."

In addition, the NCC Chairman represents the NIH on the following three DHHS Task Forces: the Interagency Task Force on Implications of the Infant Formula Code for the U.S., the Task Force on the Assessment of Scientific Evidence Relating to Problems on Infant Feeding, and the DHHS Task Force on Nutrition Objectives.

The NCC Office-Clinical Center Study on the Long-term Effect on Infants of Hypochloremic Metabolic Alkalosis Resulting from Infant Formulas Deficient in Chloride

In July 1979, a kidney specialist reported three cases of metabolic alkalosis in infants who were being fed only Neo-Mull-Soy, a soybean based formula deficient in chloride, an essential nutrient. Epidemiological work carried out by CDC found an additional 128 cases of infants who had at least one episode of metabolic alkalosis while being fed either Neo-Mull-Soy or Cho-Free, another soybean based formula deficient in chloride. (Metabolic alkalosis is an accumulation in the body of organic base compounds, such as blood bicarbonate, resulting in the derangement of the normal acid-base balance.) Analysis of formula preparations found that the products contained one-third the chloride stated on the product label and supplied approximately one-fifth the chloride recommended for infants by the American Academy of Pediatrics. The formulas were voluntarily recalled after having been on the market for about 16 months.

The NIH, at the recommendation of the NCC office, began a pilot study of infants with documented metabolic alkalosis secondary to feedings of formula deficient in chloride. In accordance with NIH policy, each child was admitted to the pilot study at the recommendation of his/her physician. The children are admitted to the study either as inpatients or outpatients. The study protocol includes a complete physical, neurological, and psychological examination along with detailed medical, social, and dietary histories. Special tests are selected in order to rule out other causes of metabolic alkalosis, especially Bartter's syndrome, which has symptoms similar to those observed in these infants.

During FY 1982, a total of 17 children who received the chloride deficient formulas and 11 siblings were admitted for studies on growth and development that included the evaluation of the renin-angiotensin aldosterone system under normal and low sodium intakes, and for studies on neurological function and behavior. Plans are being made to re-admit the children in 1983 for further evaluation and followup.

DHHS Nutrition Research Initiative

In April 1978, the Secretary of the then Department of Health, Education and Welfare, initiated a major review and reappraisal of the Department's health research activities and long-term interagency research proposals. In order to coordinate research planning and implementation, and thereby strengthen research, a steering committee consisting of representatives from the various agencies was established to define a number of health research initiatives. The initiatives were to focus on selected problem areas where mission needs of several DHHS agencies coincide with significant scientific opportunity. The health research principles approved by the Department in August 1979 were to serve as a basis in developing each initiative.

The NIH was designated as the sponsoring agency to develop the Nutrition Research Initiative, and the NCC Chairman was designated as coordinator. The agencies designated as cosponsors of the initiative were: the NIH-NCC; ADAMHA; FDA; CDC; the Office of Health Research Statistics and Technology, and NCHS-HANES. The impetus to develop this initiative in nutrition stemmed from the rapidly growing scientific interest, lively public debate on the pertinence of nutrition to particular health problems, and evolving Federal efforts to coordinate nutrition research at both policy and program levels.

The purpose of the nutrition initiative is to develop within the DHHS a more comprehensive and effective program of nutrition research and training to strengthen support of related missions. The principal thrust is to reinforce a coherent research program and to extend the growing trans-Institute cooperation in nutrition research to other DHHS agencies. A committee with members from the five agencies that conduct or support nutrition research and training are being given the task to develop a cohesive program for the Department in order to best carry out this initiative in nutrition research. This committee has the following responsibilities:

- ° Review and comment on the plans, execution, and results of research efforts, in order to refine and strengthen the Department's nutrition program;
- ° Coordinate research stemming from the obesity program, the CNRU's, nutrition research training and manpower development programs, and participation in OSTP's JSHNR;
- ° Provide information and advice on the nutrition research program to the directors of the agencies involved, to the Office of the Assistant Secretary for Health, and to the Office of the Secretary;

- ° Continuously evaluate research data and provide advice for the development of nutrition education materials for the public; and
- ° Plan and arrange for conferences, workshops, consensus development exercises, and reports as appropriate.

A number of major activities have been held under the aegis of the Nutrition Research Initiative. These include the Conference on the Assessment of Nutritional Status, the Workshop on Body Weight, Health, and Longevity, and the Joint PA for the "NIH New Investigator Research Award (NIRA) in Nutrition: ADAHMA Special Notification for Research on Nutrition and Behavior." In addition, FY 1982 marked the beginning for a new activity carried out under the Initiative. Sponsoring agencies developed and agreed upon the Human Nutrition Research Classification System, which is an important component of the congressionally-mandated Human Nutrition Research and Information Management System. A description of each activity follows:

- ° Conference on the Assessment of Nutritional Status: The Secretary, DHHS, inaugurated the Department's Nutrition Research Initiative with his keynote address at the "Conference on the Assessment of Nutritional Status" held at the NIH on September 16-18, 1981, and cosponsored by the NIH-NCC, CDC and FDA. The objective of this conference was to highlight the current state of the art in the assessment of nutritional status. This conference was described in detail on pages 105-6 of the FY 1981 Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training. The proceedings of the conference were published in the American Journal of Clinical Nutrition, May 1982, Supplement, Volume 35:1089-1325.
- ° Workshop on Body Weight, Health, and Longevity - The second step in the implementation of the Initiative was the "Workshop on Body Weight, Health, and Longevity," held January 25-26, 1982, and cosponsored by NIH-NCC and CDC. Data presented at the conference indicated that, in the United States, studies based on life insurance data (i.e., the Build and Blood Pressure Study of 1959, the Build Study 1979, the Provident Life Study), the American Cancer Society Study, and other long-term studies, such as the Framingham Heart Study and the Manitoba Study, all indicate that the weight associated with the greatest longevity tends to be below the average weight of the population under consideration, and that "slimmer is better" as long as underweight is not associated with a medical history of significant impairment and there is no evidence of calorie, protein, vitamin, or mineral deficiency, or significant medical history of impairment.

The conference participants concluded that overweight people tend to die sooner than average weight persons; this is particularly true for those who are overweight at younger ages. This effect of overweight on mortality is delayed, so that it is not seen in short-term studies. The recent analyses of the Framingham Heart Study

data emphasize that obesity is a significant independent predictor for cardiovascular disease, with smoking having an effect separate from that of overweight.

The workshop participants concluded that it is apparent that in addition to the age range of the population under examination, the interpretation of studies of body weight, morbidity, and mortality must be undertaken with consideration of the methods used to define overweight or relative weight; the exclusion for pre-existing morbid conditions; the length of observation of the subjects; and confounders in the analysis. The recommendations resulting from the conference are given below:

There is a need to develop an appropriate data base relating body weight by age, sex, and possibly frame size to morbidity and mortality, so as to permit the preparation of reference tables for defining upper limits based on morbidity and mortality statistics. Ideally, reference data should take into account appropriate attributes (physical activity level, nature of diet, etc.), as well as possible changes in the attributes. These changes will require new observational studies to quantify, in study populations, the relationship of such factors to morbidity and mortality. Therefore it is recommended that, at a minimum, the following data are needed for the development of a reference data table relating body weight to health and longevity:

The population studied should be representative of the healthy population to which the reference data will be applied.

Data on weight and height should be analyzed and presented separately by duration of followup, age, and sex, with age divided by decades. This procedure takes into account age-related changes in weight and permits establishment of age-related desirable weight goals.

Data on weight and height should also be expressed as W/H^2 with a median, range, and standard deviation presented for each age and sex group. Data so presented can be converted into tables relating weight and height, although questions remain regarding the validity of W/H^2 for estimating body fat in individuals outside the groups for which they were originally derived. Consequently, caution must be exercised in comparing W/H^2 between groups with standards not validated on the groups under consideration.

Efforts should be made to develop uncomplicated indices that correlate with the body's fat content better than does body mass index.

All statements regarding the ranges in which the morbidity and mortality are lowest should be based on statistically

significant differences in mortality rates between the nadir of the curve and the proposed limits of the range. The range should be broad enough to encompass subgroups whose life expectancy is known to differ because of certain life styles, such as smokers and nonsmokers, or whose socioeconomic status or other demographic characteristics contribute to differences in life expectancy. The expected differences contributed by such characteristics should be explicitly noted.

The value of indices of frame size should be assessed.

Since the latest Framingham data show that obesity is a significant independent predictor for cardiovascular disease, there is a need to:

Investigate the ways in which overweight becomes or acts as a "marker" for premature demise.

Identify the various types of obesity that are associated with specific diseases at different stages of the life cycle (e.g., upper trunk obesity with diabetes, fat cell number and hypertension in early adulthood, and fat cell size and hypertension in middle age).

Define the effect of duration of overweight in order to ascertain the specific age (how early in life) at which overweight becomes a marker for both morbidity and mortality.

- ° Joint PA, "NIH New Investigator Research Award (NIRA) in Nutrition: ADAMHA Special Notification for Research on Nutrition and Behavior" - It is of interest that for the first time, a joint PA "NIH New Investigator Research Award (NIRA) in Nutrition: ADAMHA Special Notification for Research on Nutrition and Behavior" published in 1981, had the support of NIH (NCI, NIADDK, NICHD, and NIDR) and another agency of the Public Health Service, the Alcohol, Drug Abuse, and Mental Health Administration. The National Institute of Alcohol Abuse and Alcoholism and the National Institute of Mental Health of ADAMHA joined NIH in encouraging new investigators to develop their research interests and capabilities in various aspects of nutrition and behavior.
- ° Human Nutrition Research and Information Management System - In December 1981, Congress directed the Secretaries of Agriculture and Health and Human Services to formulate a plan for a Human Nutrition Research and Information Management System. Section 1427 of the National Agricultural Research Extension and Teaching Policy Act of 1977 (7 U.S.C. 3177), as amended by Section 1425 of the National Agricultural Research, Extension, and Teaching Policy Act Amendments of 1981 (Title XIV of P.L. 97-98) provides as follows:

HUMAN NUTRITION RESEARCH AND INFORMATION MANAGEMENT SYSTEM Section 1427. The Secretary [of Agriculture] and the Secretary of Health and Human Services shall formulate and submit to Congress, within one hundred and eighty days after the date of enactment of this section, a plan for a human nutrition research management system. This system shall be based on on-line data support capability allowing for fiscal accounting, management, and control of cross-agency human nutrition research activities. The plan shall provide for management activities of all agencies managing funds for human nutrition research activities under existing authorities and contain recommendations for any additional authorities necessary to achieve a human nutrition research management system.

The Secretaries transmitted the plan to the Congress in July 1982. The plan states that:

The Secretaries of Agriculture and Health and Human Services agree to cooperate in the development of a Human Nutrition Research and Information Management (HNRIM) System. The two departments propose to implement this plan with the advice and assistance of the Joint Subcommittee on Human Nutrition Research (JSHNR) of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET). Initially the system will use the existing computer facilities of the HHS. However, existing computer facilities and systems supporting human nutrition Research management in the Agencies are under review to determine the best long range approach to supporting the objectives of this management information system.

The participating agencies, through the DHHS Nutrition Research Initiative, in collaboration with USDA and the JSHNR, were instrumental in the formulation of the HNRIM System plan. The JSHNR's role in the development of the plan is described in more detail on page 152 of this report.

The Joint Subcommittee on Human Nutrition Research of the Federal Coordinating Council for Science, Engineering and Technology, Office of Science and Technology Policy, Executive Office of the President

The Committee on Health and Medicine and the Committee on Agriculture, Food and Forestry Research of the Federal Coordinating Council for Science, Engineering and Technology in the Office of Science and Technology Policy (OSTP), established the Joint Subcommittee on Human Nutrition Research because of the vital importance of the benefits from human nutrition research to the welfare of the American people and the world population, and the need for nutrition research efforts of the Federal agencies to be mutually reinforcing. The JSHNR was established on September 28, 1978. At the time of its establishment, it consisted of representatives and alternates from the following eight Federal agencies and OSTP staff: Department of Health and Human Services; United States Department of Agriculture; Department of Commerce, National Oceanic

and Atmospheric Administration (DOC/NOAA); Department of Defense (DOD); Federal Trade Commission (FTC); International Development Cooperative Administration, Agency for International Development (IDCA/AID); National Science Foundation (NSF); and the Veterans Administration (VA). On March 11, 1980, the subcommittee added the National Aeronautics and Space Administration (NASA) to its membership so that the human nutrition components of the NASA-manned space flight research be included. The FTC and NASA resigned from the subcommittee at the end of FY 1982 since these two agencies no longer support nutrition research activities and do not anticipate supporting such activities in the foreseeable future. The JSHNR is presently cochaired by the NIH-NCC Chairman, who is the DHHS representative and also serves as the Executive Secretary, and the Associate Administrator, Agricultural Research Service, USDA.

The scope and the purpose of the subcommittee are as follows:

Scope: The subcommittee is concerned with: (1) all federally supported or conducted research on nutrition with emphasis on human nutrition; and (2) professional personnel needs in nutrition research and education.

This includes:

- ° Basic physiological and biochemical mechanisms for the digestion, absorption, metabolism, and transport of nutrients; the role of food ingredients in human health and performance and in the prevention and treatment of disease.
- ° Nutrient composition of foods; the effects of storage, processing, and packaging; and the biological availability of nutrients in the foods at the time of consumption.
- ° Determinants of dietary practices and methods for educating the public about dietary practices.
- ° Food consumption patterns and nutritional status of the general population and of special high-risk subgroups within the population; evaluation of the nutritional impacts of various intervention strategies and public policies.
- ° The professional personnel to carry out research on human nutrition; training programs in nutrition research and nutrition education in medical schools, dental schools, schools for allied health professionals, schools of nutrition, teachers' colleges, and schools of food and agriculture; nutrition education at the primary and secondary school level; and the manpower needs for education of the public.

Purpose: The purpose of the JSHNR is to increase the overall effectiveness and productivity of research efforts in nutrition. In fulfilling this purpose, the subcommittee will:

- a. Improve planning, coordination, and communication among Federal agencies engaged in research on nutrition.
- b. Develop and update plans for Federal research programs to meet current and future domestic and international needs for nutrition.
- c. Collect, compile, and disseminate information on nutrition research.
- d. Prepare reports describing activities, findings, and recommendations of the subcommittee.

Since the publication of its first report, Federally-Supported Human Nutrition Research, Training and Education: Update for the 1980's I. Human Nutrition Research and Training in December 1980, the subcommittee has taken major steps to enhance the coordination and planning of human nutrition research at the Federal level. These steps have been:

- (1) Development of the Human Nutrition Research Data Classification System and its modification for use as part of the Human Nutrition Research and Information Management System (HNRIM).

In order to facilitate its data collection effort, the JSHNR developed the Human Nutrition Research Data Classification System based on the definition of human nutrition research previously developed by the subcommittee. This classification system consists of 34 categories divided into the following five major areas: research in biomedical and behavioral sciences; research in food sciences; research on nutrition monitoring and surveillance of populations; research on nutrition education; and research on the effects of government policy and socioeconomic factors on food consumption and human nutrition. This classification system was adapted for use as part of the HNRIM.

The JSHNR assisted the Secretaries of Agriculture and Health and Human Services in formulating the plan for the HNRIM system as mandated by Congress in December 1981. The HNRIM system plan was submitted to Congress in July 1982, as previously described on pages 149-50 of this report.

- (2) Publication in June 1982 of two additional reports--Federally-Supported Human Nutrition Research, Training, and Education: Update for the 1980's. II. International Nutrition Research, and III. Nutrition Education Research and Professional Personnel Needs for Nutrition Education of Professionals and the Public.*

* Copies may be purchased by check or money order for \$10.50 and copies on microfiche for \$4.00 from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161; Document Numbers: PB82-231739 and PB82-231747 respectively.

In June 1982, the subcommittee published the second and third reports of the series "Federally-Supported Human Nutrition Research, Training, and Education: Update for the 1980's," thus completing this series of reports. These reports complete the overview and analysis of Federal human nutrition research and education activities and delineate critical research areas.

The second report, subtitled "II. International Nutrition Research," indicates that federally supported international nutrition research continues to be important in advancing nutritional science, in assisting in the solution of food and nutrition problems throughout the world, and in strengthening international relationships. The report includes a comprehensive review of Federal programs in international nutrition research. Two facts stand out from the review of Federal programs: "(1) a large body of high quality scientific research is being done at a very small cost to the United States; and (2) the emphasis, methods, and goals of nutrition research and education since World War II have changed from simply providing supplemental foods for the alleviation of malnutrition to developing local resources to solve local problems." Based on these considerations, the subcommittee made five recommendations regarding international human nutrition research and training.

The third and last report of this series of JSHNR reports is subtitled "III. Nutrition Education Research and Professional Personnel Needs for Nutrition Education of Professionals and the Public." The report indicates that nutrition education research has been successful in developing techniques for modifying the food intake of such different groups as individuals at high risk for cardiovascular disease and participants in the Special Supplemental Food Program for Women, Infants, and Children (WIC). To be effective, nutrition education must draw from diverse disciplines and therefore requires significant interdisciplinary cooperation. The following critical areas require emphasis if nutrition education research is to make a maximal contribution to improve the quality of life: (1) improve the knowledge about dietary practices, food consumption patterns, and their determinants; (2) develop and refine methods for informing and educating the public about the relationship of nutrition, dietary practices, and health; (3) improve the effectiveness and efficiency of nutrition education programs; and (4) expand research training and manpower development in nutrition education.

- (3) Organization of the first annual "Conference of Federally-Supported Human Nutrition Research Units--An Information Exchange Activity of the JSHNR," to be held in Washington, D.C. on December 16-17, 1982.

In response to the recommendations in the first JSHNR report to "establish an annual meeting at which the directors of the NIH Clinical Nutrition Research Units, the intramural laboratories of USDA, NIH and FDA, the VA Clinical Nutrition and Alcohol Research programs, and the managers of the DOD and NASA programs with nutrition research components will discuss research progress and future

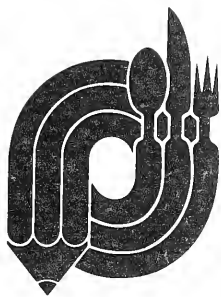
research needs," the agenda planning meeting for the first "Annual Conference of Human Nutrition Research Units--An Information Exchange Activity of the JSHNR," was held on May 10, 1982, in Washington, D.C.

Representatives of the JSHNR as well as scientists from the nutrition programs of NIH, USDA, DOD, VA, and FDA attended the meeting. The items discussed included the date, location, and appropriate format for the conference, as well as possible items to be included on the agenda such as overviews of nutrition research thrusts and achievements by the clinical nutrition research centers, areas in nutrition of congressional concern, and nutrition research areas in need of research emphasis.

The participants at the meeting agreed that a 2-day conference be held on December 16-17, 1982, in Washington, D.C., with the Honorable George W. Brown, Jr., Chairman of the Subcommittee on Department Operations, Research and Foreign Agriculture, U.S. House of Representatives, invited to present the keynote address. The agenda proposed for the conference includes presentations of nutrition research highlights on the first day by the directors of the five USDA intramural nutrition research centers, the seven NIH clinical nutrition research units, and representatives from the NIH intramural nutrition research program and the FDA intramural nutrition program.

The second day is to include presentations on the nutrition research highlights from the clinical laboratories of the VA and the research programs with nutrition components of the DOD and AID. The conference is to conclude with a general discussion to identify the strengths and gaps in nutrition research and areas for further research, as well as to make recommendations for further coordination and planning efforts in human nutrition.

Participants at the meeting also agreed that the proceedings of the conference be prepared for publication as a government document, rather than as a scientific publication. The conference proceedings will be available in 1983 through the National Technical Information Service.



IV.

APPENDICES

APPENDIX A

MANDATE OF THE NIH NUTRITION COORDINATING COMMITTEE

The Nutrition Coordinating Committee:

- ° Reviews and comments on the plans, execution, and results of pertinent Bureau, Institute, and Division research efforts relating to nutrition in order to develop the Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training.
- ° Processes and responds to incoming requests for nutrition information from the DHHS and other Federal agencies, the Executive Branch of the Government, the Congress, outside institutions, and the public.
- ° Maintains up-to-date information on funding and on intramural and extramural research and training activities in nutrition.
- ° Develops and monitors means for improving the coordination of these activities.

Within the scope of the major activities described above, the NCC has the following specific functions:

- ° To define nutrition research at the NIH. (Accomplished, see page 3.)
- ° To develop a policy statement for research and training in nutrition at the NIH. (Accomplished, see page 159.)
- ° To establish information exchange. Each representative presents to the NCC any new plans, activities, conferences, and workshops that are concerned with nutrition. Future workshops and conferences are discussed to ensure full participation of all relevant Institutes; when many Institutes are involved, the NCC sponsors or cosponsors such workshops or conferences. Through the information exchange mechanism, the NCC identifies areas of collaboration for further research. The NCC informs the NIH nutrition community of all meetings, both within and outside NIH, concerned with nutrition. The committee, if requested, also reviews and comments on nutrition reports generated by the NIH and by other Federal and non-Federal agencies.
- ° To develop a data retrieval system for research and training in nutrition. (Accomplished, see page 5.)
- ° To review proposed legislation and regulations. The NCC develops mechanisms for receiving, reviewing, and distributing information on proposed legislation affecting nutrition policy.
- ° To develop and maintain effective liaison with other departments and agencies that have nutrition activities. The NCC assesses existing liaison mechanisms and identifies those departments and agencies requiring a liaison relationship. Liaison representatives provide information to the NCC.

- ° To encourage the application of nutrition research to practice. The NCC members identify research data that are ready for "technology transfer" and promote the appropriate application of new knowledge in nutrition.
- ° To promote the dissemination of information for the purpose of public education on the role of nutrition on health and disease. The NCC assists in coordinating Bureau, Institute, and Division efforts in nutrition education and acts as a focal point for the dissemination of nutrition information to the public.

NUTRITION POLICY OF THE NIH

Policy Objectives:

The NIH supports DHHS policy by sponsoring and conducting biomedical research designed to improve the quality of life for all Americans through optimal nutrition. Basic biomedical nutrition research will develop knowledge needed to promote and maintain health, as well as to prevent and treat disease.

Nutrition research has passed through two stages and is now entering a third. The first stage saw the discovery of vitamins and the development of many of the basic nutritional requirements. The second stage reduced nutrition to subcellular and molecular terms within areas of biochemistry and physiology. The third stage calls for a synthesis of newer findings for translation into practical information to assist the individual to develop normally, to avoid disease, and to live as long and as healthy a life as possible. For this third stage, knowledge is needed that will permit distinction among individuals in terms of genetic differences that affect dietary requirements.

Areas of Emphasis:

Current nutrition research at NIH concentrates on eight critical areas:

1. Clinical Nutrition Throughout the Life Cycle. Research in this initial area examines variations in nutritional requirements to promote and maintain health during all phases of the life cycle. Within the clinical nutrition program, research is also directed towards elucidating the effects of infant feeding practices and infant nutrition on subsequent physiological, immunological, and mental development. Another research goal involving the life cycle is to understand the effects of maternal nutritional status and maternal diet before and during pregnancy on the development of the fetus. In order to understand the ramifications of this nutritional problem, more must be learned about the interaction between the genetic makeup of an individual and his dietary intake. Special emphasis is given to studies on the role of nutrition in health of the aged and aging process, particularly the effects of aging on nutrient utilization, digestion, absorption, and metabolism, and nutrition and age-related mental deterioration.
2. Role of Nutrition in Disease Development. The NIH conducts research on mechanisms by which dietary deficiencies, imbalances, and excesses lead to the development of physical and mental diseases and disorders.
3. Prevention of Disease. The NIH has assumed a leading role in shifting the emphasis in nutrition research from curing disease after symptoms have developed to preventing or delaying the onset of disease. Continued research emphasis is given to malnutrition in all its guises, including under- and over-nutrition, obesity, food faddism, and specific dietary deficiencies.

4. Treatment of Disease. The NIH develops nutritional therapies for specific diseases, such as cancer, gastrointestinal disorders, obesity, osteoporosis, renal insufficiency, atherosclerosis, and inborn errors of metabolism. Improved methods are being developed to provide general nutritional support for newborns of low-birth-weight who may require parenteral supplementation and for elderly, disease-ridden, traumatized, or post-operative patients who may require total parenteral nutrition or elemental diets.
5. Technology Transfer. An important component of the NIH nutrition policy is to assure appropriate application of research in practice. To expedite transfer of nutrition technology, the NIH is establishing mechanisms to evaluate research data relevant to nutrition and public health.
6. Nutrition Education. The NIH continues to support research in nutrition education as by-products of clinical trials and demonstration projects; by the education of the physician through professional societies, scientific meetings, and journals; and by the production of nutrition education materials for the health educator and the public. Encouragement of positive nutrition behavior is an obvious task for educators of children, young adults, and the elderly.
7. Research Training. The NIH encourages and supports the teaching of modern biochemical nutrition at the pre- and postdoctoral levels. This training includes the disciplines upon which nutrition research is based, such as gastroenterology, endocrinology, metabolism, developmental biochemistry, genetics, and molecular biology. The NIH also promotes expanded training programs in basic and clinical nutrition research aimed principally at the physician investigator and clinically oriented biomedical scientists.
8. Coordination. The NIH cooperates in establishing mechanisms for interagency coordination. Nutrition research at the NIH is coordinated through the Nutrition Coordinating Committee. Institutes initiate their own nutrition programs within their appropriated budgets. The committee seeks agreement on critical issues of definition, comments upon individual programs identified to it, maintains an information exchange (mechanisms for program development), promotes liaison with other Federal agencies, and encourages coordinated program planning among Institutes and with other appropriate agencies. The committee assists in the development of nutrition data retrieval systems, and reviews legislative and regulatory initiatives that impact upon human nutrition research.

APPENDIX C

FY 1982 NUTRITION EXPENDITURES BY INSTITUTE AND DIVISION

Table C-1

National Cancer Institute
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

		Breakdown		Total	
	Item	Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular	315	16,258		
	Clinical trials . .	96	1,126		
	Total			411	17,384
Program projects:	Regular	22	4,017		
	Clinical trials . .	2	587		
	Total			24	4,604
Contracts:	Regular	89	3,509		
	Clinical trials . .	8	151		
	Total			97	3,660
Centers:	Regular	26	1,852		
	Clinical trials . .	0	0		
	Total			26	1,852
Research Resources Support				0	0
Reimbursement agreements				7	642
Research Career Development Awards				11 *	329
New Investigator Research Awards				7 *	211
Training:	Training grants . .	17 *	318		
	Fellowships	0 *	0		
	Total			17 *	<u>318</u>
Subtotal - Extramural					\$ 29,000
<u>Intramural</u>					
Projects				20	1,553
Training				0 *	<u>0</u>
Subtotal - Intramural					\$ 1,553
TOTAL NUTRITION RESEARCH AND TRAINING - NCI					\$ 30,553

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-2

National Heart, Lung, and Blood Institute
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

		Breakdown		Total	
	Item	Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular	144	14,598		
	Clinical trials . .	8	4,261		
	Total			152	18,859
Program projects:	Regular	13	4,915		
	Clinical trials . .	0	0		
	Total			13	4,915
Contracts:	Regular	8	257		
	Clinical trials . .	19	1,976		
	Total			27	2,233
Centers:	Regular	14	6,825		
	Clinical trials . .	0	0		
	Total			14	6,825
Research Resources Support				0	0
Reimbursement agreements				7	421
Research Career Development Awards				5 *	82
New Investigator Research Awards				10 *	277
Training:	Training grants . .	91 *	828		
	Fellowships	0 *	0		
	Total			91 *	828
Subtotal - Extramural					\$ 34,439
<u>Intramural</u>					
Projects				8	876
Training				6 *	133
Subtotal - Intramural					\$ 1,009
TOTAL NUTRITION RESEARCH AND TRAINING - NHLBI.					\$ 35,449

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-3

National Institute of Dental Research
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

	Item	Breakdown		Total	
		Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular	8	397		
	Clinical trials . .	0	0		
	Total			8	397
Program projects:	Regular	1	74		
	Clinical trials . .	0	0		
	Total			1	74
Contracts:	Regular	4	572		
	Clinical trials . .	0	0		
	Total			4	572
Centers:	Regular	1	198		
	Clinical trials . .	0	0		
	Total			1	198
Research Resources Support				0	0
Reimbursement agreements				0	0
Research Career Development Awards				1 *	33
New Investigator Research Awards				1 *	17
Training:	Training grants . .	7 *	94		
	Fellowships	3 *	86		
	Total			10 *	<u>180</u>
Subtotal - Extramural					\$ 1,471
<u>Intramural</u>					
Projects				5	58
Training				0 *	<u>0</u>
Subtotal - Intramural					\$ 58
TOTAL NUTRITION RESEARCH AND TRAINING - NIDR					\$ 1,529

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-4

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases
 BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
 (in thousands of dollars)

Extramural	Item	Breakdown		Total	
		Number	Cost	Number	Cost
Research grants:	Regular	406	19,484		
	Clinical trials	8	49		
	Total			414	19,533
Program projects:	Regular	12	1,613		
	Clinical trials	0	0		
	Total			12	1,613
Contracts:	Regular	8	154		
	Clinical trials	0	0		
	Total			8	154
Centers:	Regular	6	2,084		
	Clinical trials	0	0		
	Total			6	2,084
Research Resources Support				0	0
Reimbursement agreements				0	0
Research Career Development Awards				14 *	369
New Investigator Research Awards				22 *	681
Training:	Training grants	66 *	763		
	Fellowships	21 *	198		
	Total			87 *	961
Subtotal - Extramural					\$ 25,395
Intramural					
Projects				23	1,481
Training				9 *	105
Subtotal - Intramural					\$ 1,586
TOTAL NUTRITION RESEARCH AND TRAINING - NIADDK					\$ 26,981

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-5

National Institute of Neurological and
Communicative Disorders and Stroke
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

Extramural	Item	Breakdown		Total	
		Number	Cost	Number	Cost
Research grants:	Regular	39	2,059		
	Clinical trials . .	0	0		
	Total			39	2,059
Program projects:	Regular	5	529		
	Clinical trials . .	1	19		
	Total			6	548
Contracts:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Centers:	Regular	4	181		
	Clinical trials . .	0	0		
	Total			4	181
Research Resources Support				0	0
Reimbursement agreements				0	0
Research Career Development Awards				0 *	0
New Investigator Research Awards				1 *	51
Training:	Training grants . .	0 *	0		
	Fellowships	0 *	0		
	Total			0 *	0
Subtotal - Extramural					\$ 2,839
Intramural					
Projects					0
Training				*	0
Subtotal - Intramural				\$	0
TOTAL NUTRITION RESEARCH AND TRAINING - NINCDS					\$ 2,839

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-6

National Institute of Allergy and Infectious Diseases
 BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
 (in thousands of dollars)

	Item	Breakdown		Total	
		Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular	25	1,561		
	Clinical trials . .	0	0		
	Total			25	1,561
Program projects:	Regular	1	17		
	Clinical trials . .	0	0		
	Total			1	17
Contracts:	Regular	1	21		
	Clinical trials . .	0	0		
	Total			1	21
Centers:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Research Resource Support				0	0
Reimbursement agreements				0	0
Research Career Development Awards				1 *	18
New Investigator Research Awards				2 *	80
Training:	Training grants . .	9 *	8		
	Fellowships	1 *	6		
	Total			10 *	<u>14</u>
Subtotal - Extramural					\$ 1,711
<u>Intramural</u>					
Projects				1	118
Training				2 *	<u>24</u>
Subtotal - Intramural					\$ 142
TOTAL NUTRITION RESEARCH AND TRAINING - NIAID					\$ 1,853

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-7

National Institute of General Medical Sciences
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

Extramural	Item	Breakdown		Total	
		Number	Cost	Number	Cost
Research grants:	Regular	7	663		
	Clinical trials . .	0	0		
	Total			7	663
Program projects:	Regular	1	188		
	Clinical trials . .	0	0		
	Total			1	188
Contracts:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Centers:	Regular	4	689		
	Clinical trials . .	0	0		
	Total			4	689
Research Resources Support				0	0
Reimbursement Agreements				0	0
Research Career Development Awards				1 *	40
New Investigator Research Awards				1 *	11
Training:	Training grants . .	77 *	250		
	Fellowships	0 *	0		
	Total			77 *	250
Subtotal - Extramural					\$ 1,841
<u>Intramural</u>					
Projects					0
Training				*	0
Subtotal - Intramural					\$ 0
TOTAL NUTRITION RESEARCH AND TRAINING - NIGMS					\$ 1,841

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-8

National Institute of Child Health and Human Development
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

		Breakdown		Total	
	Item	Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular	129	9,354		
	Clinical trials . .	7	804		
	Total			136	10,158
Program projects:	Regular	13	2,064		
	Clinical trials . .	3	1,072		
	Total			16	3,136
Contracts:	Regular	10	1,258		
	Clinical trials . .	1	290		
	Total			11	1,548
Centers:	Regular	11	415		
	Clinical trials . .	0	0		
	Total			11	415
Research Resources Support				2	41
Reimbursement agreements				0	0
Research Career Development Awards				10 *	361
New Investigator Research Awards				8 *	371
Training:	Training grants . .	19 *	154		
	Fellowships	6 *	56		
	Total			25 *	<u>210</u>
Subtotal - Extramural					\$ 16,240
<u>Intramural</u>					
Projects				13	1,930
Training				7 *	<u>186</u>
Subtotal - Intramural					\$ 2,116
TOTAL NUTRITION RESEARCH AND TRAINING - NICHD					\$ 18,356

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-9

National Eye Institute
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

<u>Extramural</u>	<u>Item</u>	<u>Breakdown</u>		<u>Total</u>	
		<u>Number</u>	<u>Cost</u>	<u>Number</u>	<u>Cost</u>
Research grants:	Regular	84	4,201		
	Clinical trials . .	0	0		
	Total			84	4,201
Program projects:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Contracts:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Centers:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Research Resources Support				0	0
Reimbursement agreements				0	0
Research Career Development Awards				3 *	44
New Investigator Research Awards				5 *	111
Training:	Training grants . .	0 *	0		
	Fellowships	3 *	47		
	Total			3 *	47
Subtotal - Extramural					\$ 4,403
<u>Intramural</u>					
Projects				10	853
Training				0 *	0
Subtotal - Intramural					\$ 853
TOTAL NUTRITION RESEARCH AND TRAINING - NEI					\$ 5,256

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-10

National Institute of Environmental Health Sciences
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

<u>Extramural</u>	<u>Item</u>	<u>Breakdown</u>		<u>Total</u>	
		<u>Number</u>	<u>Cost</u>	<u>Number</u>	<u>Cost</u>
Research grants:	Regular	17	983		
	Clinical trials . .	0	0		
	Total			17	983
Program projects:	Regular	1	439		
	Clinical trials . .	0	0		
	Total			1	439
Contracts:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Centers:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Research Resources Support				0	0
Reimbursement agreements				0	0
Research Career Development Awards				0 *	0
New Investigator Research Awards				0 *	0
Training:	Training grants . .	0 *	0		
	Fellowships	0 *	0		
	Total			0 *	0
Subtotal - Extramural					\$ 1,422
<u>Intramural</u>					
Projects				1	160
Training				0 *	0
Subtotal - Intramural					\$ 160
TOTAL NUTRITION RESEARCH AND TRAINING - NIEHS					\$ 1,582

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-11

National Institute on Aging
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

		Breakdown		Total	
	Item	Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular	25	1,580		
	Clinical trials . .	0	0		
	Total			25	1,580
Program projects:	Regular	8	965		
	Clinical trials . .	0	0		
	Total			8	965
Contracts:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Centers:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Research Resources Support				0	0
Reimbursement agreements				1	180
Research Career Development Awards				12 *	85
New Investigator Research Awards				3 *	90
Training:	Training grants . .	30 *	4		
	Fellowships	2 *	22		
	Total			32 *	<u>26</u>
Subtotal - Extramural					\$ 2,926
<u>Intramural</u>					
Projects				5	335
Training				0 *	<u>0</u>
Subtotal - Intramural					\$ 335
TOTAL NUTRITION RESEARCH AND TRAINING - NIA					\$ 3,261

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

Table C-12

Division of Research Resources
BIOMEDICAL AND BEHAVIORAL NUTRITION RESEARCH AND TRAINING, FY 1982
(in thousands of dollars)

	Item	Breakdown		Total	
		Number	Cost	Number	Cost
<u>Extramural</u>					
Research grants:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Program projects:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Contracts:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Centers:	Regular	0	0		
	Clinical trials . .	0	0		
	Total			0	0
Research Resources Support				260	14,823
Reimbursement agreements				0	0
Research Career Development Awards				0 *	0
New Investigator Research Awards				0 *	0
Training:	Training grants . .	0 *	0		
	Fellowships	0 *	0		
	Total			0 *	<u>0</u>
Subtotal - Extramural					\$ 14,823
<u>Intramural</u>					
Projects				0	0
Training				0 *	<u>0</u>
Subtotal - Intramural				0	\$ 0
TOTAL NUTRITION RESEARCH AND TRAINING - DRR					\$ 14,823

*Number of persons.

NOTE: Only that component of each project identified as nutrition research according to the NIH definition of nutrition research is included in the cost figure.

APPENDIX D

LEGISLATIVE AUTHORITY OF NIH FOR HUMAN NUTRITION RESEARCH

Two Institutes have specific mandates to conduct nutrition research at the NIH. Those mandates are as follows (references are to PHS Act):

NCI: Section 407(b)(4)--"Collect, analyze, and disseminate information (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer) useful in the prevention, diagnosis, and treatment of cancer, including . . ."

NHLBI: Section 413(a)(1)--"investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences . . ."

Section 413(d)--"There shall be in the Institute an Assistant Director for Prevention, Education and Control . . . In the conduct of such a program, special emphasis shall be placed upon dissemination of information regarding diet, exercise, stress, cigarette smoking, weight control . . ."

Other Institutes that conduct and support nutrition research do so under much broader authority. Each conducts research programs in the "diagnosis, prevention, and treatment" of specific diseases and life processes within their areas of responsibility. Those authorities are as follows:

General authority	Section 301
International cooperation authority	Section 307
Training authority	Section 472(a)(1)(a)
NCI	Section 402(a)
NHLBI	Section 412(1)
NIDR	Section 422(a)
NIADDK	Section 434(c) Section 435(a) Section 439(a)
NICHD	Section 441(a)
NIGMS	Section 442
NIA	Section 464
Other Institutes	Section 431(b)

NCI LEGISLATIVE AUTHORITY FOR NUTRITION INFORMATION
AND EDUCATION PROGRAMS

The specific mandates of the NCI for nutrition information and education programs are contained in Section 407(b)(4) of Public Law 92-218, "The National Cancer Act of 1971," as amended in Public Law 93-352, "Title I - Extension of Cancer Program":

P.L. 92-218, Section 407(b)(4): "Collect, analyze, and disseminate all data useful in the prevention, diagnosis, and treatment of cancer, including the establishment of an international cancer research data bank to collect, catalog, store, and disseminate insofar as feasible the results of cancer research undertaken in any country for the use of any person involved in cancer research in any country."

P.L. 93-352, Section 103: "Section 407(b)(4) of the Public Health Service Act is amended by striking out 'all data' and inserting in lieu thereof 'information (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer).'"

NHLBI LEGISLATIVE AUTHORITY FOR NUTRITION INFORMATION
AND EDUCATION PROGRAMS

The specific mandates of the NHLBI for nutrition information and education programs can be found in Section 413 of the Public Health Service Act, March 1977. This Section indicates the general plan for the Institute to expand, intensify, and coordinate the Institute's activities in the areas of heart, blood vessel, lung, and blood diseases and blood resources. To implement this mandate, Section 413(a)(1) states:

"Investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases."

Section 413(d) states the following:

"There shall be in the Institute an Assistant Director for Prevention, Education, and Control who shall be appointed by the Director of the Institute. The Director of the Institute, acting through the Assistant Director for Prevention, Education, and Control, shall conduct a program to provide the public and the health professions with health information with regard to cardiovascular and blood and pulmonary diseases and blood resources. In the conduct of such program, special emphasis shall be placed upon dissemination of information regarding diet, exercise, stress, hypertension, cigarette smoking, weight control, and other factors affecting the prevention of arteriosclerosis and other cardiovascular diseases and of pulmonary and blood diseases."

DISCRIMINATION PROHIBITED: Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participating in, be denied benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the Nutrition Coordinating Committee must be operated in compliance with these laws and Executive Orders.



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10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

